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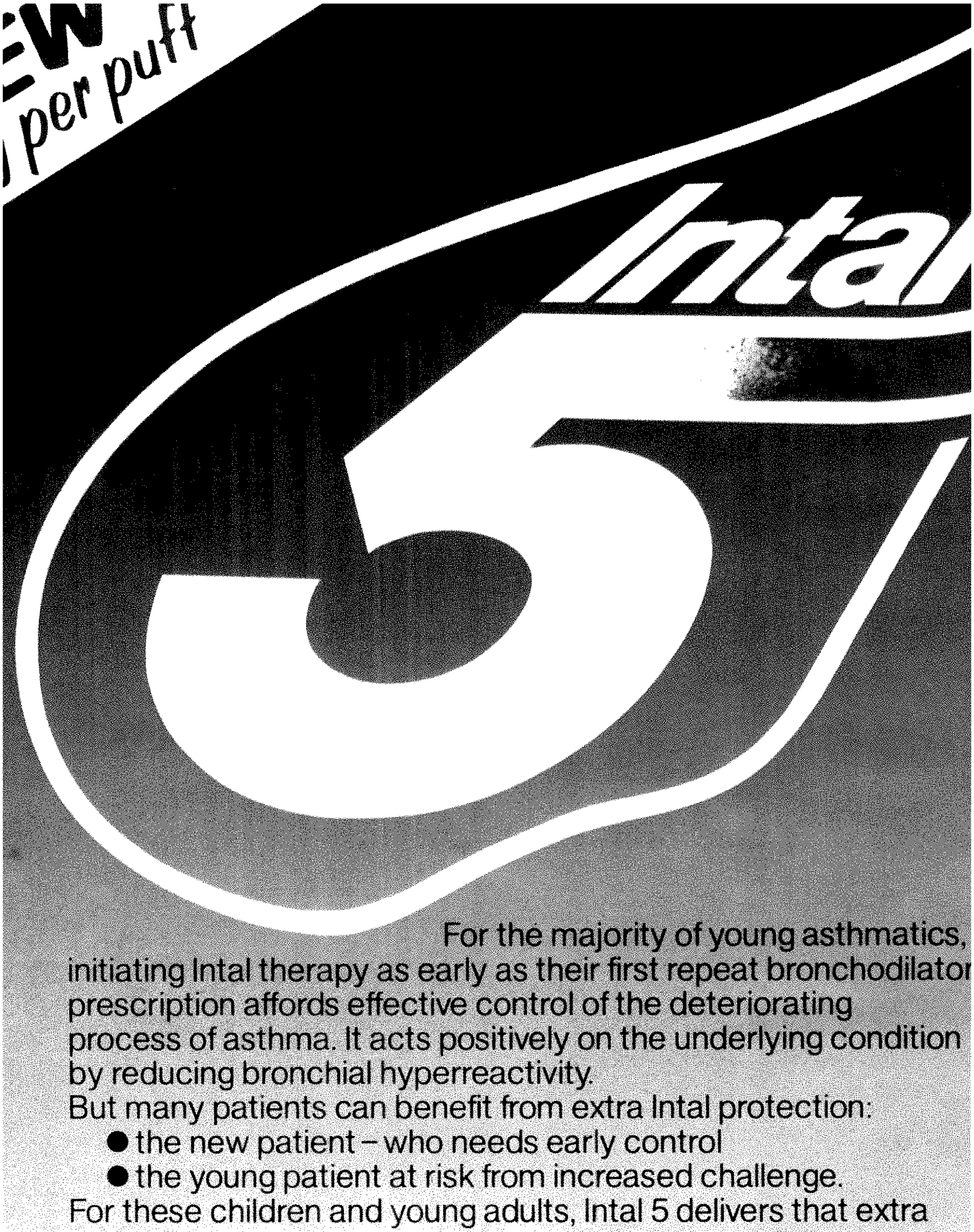

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Annotations

Artificial urinary sphincters

Artificial sphincters have been in the news recently, in both the lay press (and specifically on the radio) and the medical press. As a result there has been a surge of interest from various 'pressure groups', such as the Association for Spina Bifida and Hydrocephalus and the Multiple Sclerosis Society, and patients are now asking their medical advisers for information on the subject, particularly those who have heard, through their societies, or know of others who have been treated with these devices.

The only type of artificial sphincter that has received a general recommendation among urologists is the Brantley Scott artificial urinary sphincter (AUS), which is produced in the USA by American Medical Systems, Inc. None of the other currently available devices can be recommended and will not, therefore, be discussed further.

Brantley Scott artificial urinary sphincter

The Brantley Scott artificial urinary sphincter consists of a fluid filled cuff that is wrapped around the bladder neck in either boys or girls, or the bulbar urethra in boys, to provide a circumferential occlusive force. The pressure within the cuff is determined by a pressure regulating balloon connected to the cuff by means of a control pump. The control pump may be a single component (AS 800) or two separate components (the control assembly being one, the pump the other: AS 791/792) depending on which particular model of the device is being implanted. The function of the control assembly is to regulate the flow of fluid between the cuff and the balloon, which is always from balloon to cuff, thereby providing the occlusive force. When the pump is squeezed two or three times, however, thereby reversing the direction of fluid flow so that the cuff is emptied into the pressure balloon, the occlusive force is removed thus allowing the patient to void. The cuff then refills spontaneously from the pressure balloon over a three to five minute period, by virtue of the valve arrangement within the control assembly, thereby restoring the occlusive force.

The cuffs come in various lengths so that each device can be accurately fitted in its desired location, and the pressure regulating balloons are precalibrated during manufacture to produce pressures within specified ranges, so that in each patient an occlusive force appropriate to the local tissue characteristics can be chosen by the implanting surgeon. The entire device is internal and therefore

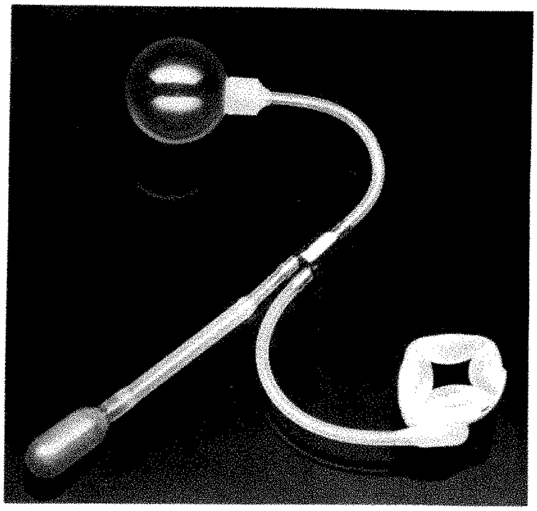

Fig. 1 *Brantley Scott Sphincter (AS791/792)*

The pump on the left is placed in the scrotum or the labium majus.

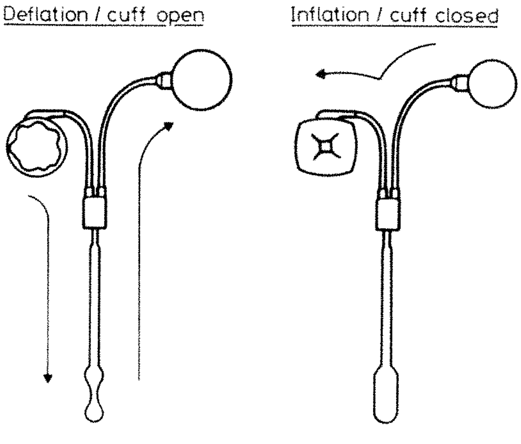

Fig. 2 *Diagram of mode of action.*

invisible; the pump is sited in the scrotum or labium majus to make it accessible to the patient. The smaller size of the pump in the model which has the control assembly and the pump as two separate components (AS 791/792 make that particular model more suitable for children.

Effectiveness of the sphincter

The models currently available are derived from an original model that was first implanted in 1971, and there have been several intermediate stages in their development. Overall, there are therefore 15 years of experience with the artificial urinary sphincter, although most implants, particularly in Britain and with currently available models, have occurred in the past five years. With this in mind, it is probably best not to assess the durability of the device in relation to the overall 15 year experience, but to assess its effectiveness in relation to the results over the past five years, during which time more than 2000 devices have been implanted worldwide.

There is no argument that the sphincter is an extremely effective way of dealing with incontinence caused by weakness of the natural sphincter mechanisms, when that is the only cause of incontinence. Most centres show at least a 75% long term cure rate in these cases. Factors that lead to concern are the problems and complications of the device, the cost effectiveness of the artificial sphincter compared with other forms of treatment for sphincter weakness incontinence, its role in the overall treatment of incontinent patients, and the logistic problems raised by all these factors when one comes to consider the provision of an incontinence service for a community.

Problems and complications

The problem with the artificial urinary sphincter is that of providing sufficient occlusive force to give continence without impairing the blood flow to the tissues being compressed to a degree that would lead to erosion of the cuff through those tissues. Erosion is mainly a problem in the elderly, and therefore is usually seen in patients who have had an artificial urinary sphincter for incontinence after prostatectomy. In younger patients, usually children with spina bifida, this is rare, particularly if a few weeks are allowed to elapse between implantation and activation of the device, to allow the local tissue response to surgery to resolve before the cuff is pressurised. Thus, although the overall continence rate after implantation is 75%, the success rate is about 90% in the younger age group.

By contrast, insufficient pressure leads to residual stress incontinence, and this is seen in about 10% of patients. It is treated by replacing the pressure balloon with one with a higher pressure range, and this almost invariably cures the problem.

Additional complications are rare, and are mainly infection, which is largely prevented by meticulous preoperative preparation and perioperative care to avoid contamination at the time of implantation, and mechanical failure, usually due to leakage of fluid from the system. The latter obviously requires replacement of the defective component and fortunately occurs in only 2 or 3% of patients.

Cost effectiveness

An artificial urinary sphincter costs about £2000 at current rates of exchange. This is expensive but doubtless will cost less when there are equally effective alternative devices on the market. Nonetheless, the cost of providing protective pants and absorptive pads or long term stoma care as alternatives makes an artificial urinary sphincter cost effective after about five years, over and above any other considerations relating to the desirability of continent urethral voiding.

Who should have it

The artificial urinary sphincter is a treatment for sphincter weakness only—and then only when other methods fail or are inappropriate. In general, non-neuropathic sphincter weakness incontinence can usually be treated without recourse to this device, and neuropathic sphincter weakness incontinence is commonly associated with abnormalities of detrusor function. It is therefore mandatory for all patients, and particularly those with neuropathic dysfunctions, to have a full videourodynamic evaluation as part of their preoperative assessment to identify detrusor abnormalities and, if at all possible, for any of these abnormalities to be treated before implantation of an artificial urinary sphincter.

Urodynamic factors are not the only ones that have to be considered. The largest single group for whom an artificial urinary sphincter may be considered is the group of children and young adults with congenital cord lesions. Traditionally, incontinence in this group has been treated either by pads, appliances, or indwelling catheters on the one hand or by urinary diversion on the other. The artificial urinary sphincter provides an alternative method of management which gets rid of the need for the former but avoids the 'stigma' of the latter; hence its attractiveness to the 'pressure groups' referred to earlier. On the other hand, irrespective of the high incidence of multiple urodynamic abnormalities in these patients and the consequent need for additional surgical procedures to deal with these, which the patient's general condition may mitigate against, there is the need to consider the factor, common in this group, of the general desirability for continence in a patient confined to a wheelchair. Given that it is usually fairly easy to provide 'social dryness' in these patients (particularly boys) with appliances and catheters, thereby avoiding the need for the regular and maybe frequent transfer from wheelchair to an appropriate toilet and back again, the artificial urinary sphincter and other types of reconstructive surgery are probably best reserved for patients who are mobile, unless, particularly in girls, conservative methods of management have failed.

Logistic problems

It follows from the above considerations that to provide a complete service for the treatment of incontinence and related voiding dysfunctions, a unit must be able to provide full videourodynamic investigations and have the ability to perform not just artificial urinary sphincter implantation but also all the other surgical procedures that may be necessary for the functional reconstruction of the urinary tract. These require special expertise and experience that are really only to be found in specialised centres with the necessary surgical and urodynamic expertise and the equally necessary nephrological, neurological, radiological, and anaesthesiological back up. Unfortunately, there are very few of these centres at present and many patients therefore have to travel some distance if they are to get adequate management of their problem.

Conclusion

The artificial urinary sphincter is a very effective way of eliminating sphincter weakness incontinence when other methods fail or are inappropriate, but is only one of a number of techniques that are currently available for the functional reconstruction of the urinary tract. These techniques require investigational and technical expertise that are to be found only in specialised centres, which are few and far between and are obviously expensive in both staff and equipment. This expenditure, however, is more than offset by the long term cost effectiveness of the artificial sphincter when compared with the alternative of providing pads, appliances, and stoma care for the lifelong management of children with neuropathic incontinence, who form the largest group for whom this treatment is applicable.

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Archives of Disease in Childhood, 1986, **61,** 4–5

Chemoprophylaxis of meningitis

'If it is preventable, why not prevent it?' is a legitimate starting point in the discussion of infections, particularly communicable infections. How does this aphorism stand in regard to meningococcal and *Haemophilus influenzae* meningitis? Although vaccines are available and licensed in the United States for protection against infection with meningococci (Sero groups A, C, Y, and W135 but not B)[1] and *H influenzae* type B,[2] they are not generally available in the United Kingdom, and prevention of these forms of meningitis relies on chemoprophylaxis.

Meningococcal meningitis has long been recognised as infectious—that is, communicable from one individual to another; worldwide epidemics are part of the published reports. The organism resides in the nasopharynx of a proportion of the population who are for the most part asymptomatic, and droplet spread is responsible for communication to other subjects, a tiny proportion of whom, susceptible in an ill understood way, develop invasive disease. Crowded living conditions, as in barracks, leads to increasing acquisition rates of meningococci and a rising incidence of meningitis. The prevention of colonisation and, by implication, invasion by meningococci, would therefore seem a rational aim, and this is the theoretical basis for the present policy of administering antibacterial agents to close contacts of known cases. Plausible though the policy appears, is it practical and does it work? It is certainly practical in the sense that drugs (rifampicin, sulphonamides, and minocycline), when administered to controls, do reduce carriage and the incidence of disease. We know that 70% of secondary cases of meningococcal meningitis occur within one week of the confirmation of the index case; it could therefore be argued that what is really happening in the context of chemoprophylaxis is that very early cases are being treated, but it should be pointed out that penicillin, which is so effective in treatment of cases, does not prevent carriage or indeed the development of invasive disease when it is used prophylactically. It may be that the pharmacodynamics of individual drugs is responsible for their usefulness or otherwise in prophylaxis. Rifampicin, sulphonamide, and minocycline reach fairly high concentrations in the saliva, whereas penicillin does not. Rifampicin or sulphonamide (where sensitive strains are present) are now recommended as chemoprophylaxis in children and adults in the following doses: rifampicin: adults 600 mg twice daily for two days, children (aged over 1 month) 10 mg/kg every 12 hours for two days, children (aged under 1 month) 5 mg/kg every 12 hours for two days; sulphadiazine or sulphadimidine 0·5–1 g every eight hours for three days. Combining rifampicin and sulphonamide effects a higher clearance rate but increases side effects.

To whom should chemoprophylaxis be offered? Certainly close family contacts, particularly those sleeping in the same room; close school contacts but not the whole class; nurses in constant close contact and perhaps medical staff only where there has been mucous membrane contact. Judgment on what other groups might be included for chemoprophylaxis may be helped by recognising that approximate relative risks for different groups are as follows: if pre-elementary school contacts represent a risk factor of 1, day care nursery contacts are 5 and household contacts are 9.[3] A case can also be made for routine chemoprophylaxis in patients before discharge from hospital when curative treatment of meningococcal or influenzal meningitis is completed.

Turning to *H influenzae* type B meningitis, we note some similarities but also some striking differences from meningococcal infection. The organism responsible is the type B encapsulated strain and is again a respiratory resident, and one might conclude that outbreaks or epidemics would be well documented, but this is not so. Occasionally, instances of multiple cases of meningitis have been reported in the same family since 1909[4–6] and in the day care centres,[7 8] and this led to a national study of secondary spread in household contacts in America, published in 1979.[9] In this study Ward *et al* obtained prospective data in 19 states of America in which *H influenzae* meningitis was reported in 1403 patients, and 82% of the exposed families were investigated for the occurrence of *H influenzae* disease within 30 days after onset of illness in the index case. The risk to children less than 1 year old was 6%, and in those less than 4 was 2%. None of the 2624 contacts above the age of 5 was affected. The authors concluded that the risk of *H influenzae* disease in household contacts under 6 years of age was similar to the risk of secondary meningococcal disease in all household contacts.

It is for the most part on these American data that the rationale for chemoprophylaxis in *H influenzae* infections resides. We note the restricted age incidence, which makes large families, day care centres, and other areas where young children collect as representing special epidemiological situations deserving attention when prophylaxis is considered. Here is a major difference in regard to meningococcal infection, which, although more common in young children, attacks young adults and indeed all age groups. There are also differences between the American and the British experience. *H influenzae* meningitis is the commonest cause of bacterial meningitis in the US, resulting in perhaps 8000 cases each year. In the UK meningococci still account for the majority of notified cases, although in recent years the proportion of cases due to *H influenzae* is increasing. Although it is extremely difficult and perhaps unwise to compare statistics on meningitis, nonetheless the impression is that *overall* mortality is greater in the US than in the UK for *H influenzae* meningitis; in one large hospital series from Edinburgh there was not one single death in 91 cases reported from 1950–79.[10]

In the UK we lack precise epidemiological information on the incidence of secondary cases of *H influenzae* meningitis. The only reliable information is an unpublished survey conducted by the Public Health Laboratory Service in which only 11 instances of secondary infection were identified over a 10 year period. If this low secondary attack rate is confirmed, it suggests that meningitis due to *H influenzae* behaves differently in the UK and the US and that American experience in chemoprophylaxis (using mostly rifampicin) may have limited application in Britain. Until we have much firmer evidence, what policy should be adopted for chemoprophylaxis when confronted by an infant with *H influenzae* meningitis? Immediate contacts under 4 years might reasonably be offered rifampicin in doses of 20 mg/kg/day for four days. Two points to note about chemoprophylaxis are that doses of 10 mg/kg/day for four days have little effect,[11] and that meningitis can occur even in children who have received prophylactic treatment.[12] Careful clinical surveillance of susceptible infants remains paramount.

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Archives of Disease in Childhood, 1986, **61,** 6–10

Original articles

Deaths from asthma in New Zealand

M R SEARS, H H REA, J FENWICK, R BEAGLEHOLE, A J D GILLIES, P E HOLST, T V O'DONNELL, R P G ROTHWELL, AND D C SUTHERLAND

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SUMMARY We report the first complete population based study of childhood deaths due to asthma. All deaths ascribed to asthma in New Zealand children aged 0–14 were investigated as part of a two year national study of mortality from asthma. The 16 children who died from asthma all developed asthma by the age of 4; 15 had a family history of asthma, and 12 had associated atopic disorders. Disturbed pyschosocial relationships were evident in eight families. Seven children died in less than three hours from the onset of their final attack. All children died outside hospital. Mortality from asthma in Maori children (3·14 per 100 000) was five times that of European children. With hindsight, factors which if avoided could have led to a different outcome were identified in eleven cases. The circumstances surrounding these deaths were similar to those described for adults with asthma; this study, however, underlines the importance of parental care and knowledge in the management of children with asthma. Inadequate long term medical care, underassessment of severity by family and doctors, failure of the family to call for help when required, and inadequate responses of medical services contributed to the fatalities. Excess beta_2 sympathomimetic dosage or overreliance on home nebulisers were uncommon. Most childhood deaths from asthma should be prevented by increased family awareness, better assessment of severity, improved long term treatment, and rapid access to emergency medical care.

Asthma is a rare cause of childhood mortality. However, an increase in mortality in young New Zealand asthmatics noted first in 1977 and continuing over the next five years caused concern.[1] The increase brought the New Zealand mortality rate for childhood asthma to over three times that of the United Kingdom.[2] Interaction between newly available sustained release theophylline and inhaled beta agonist was suggested as a possible reason for the rising mortality.[3] Few series of childhood asthma deaths have been reported, and, apart from one community based study of 30 deaths over a period of 20 years,[4] all have been hospital based populations.[5–8]

This paper reviews all deaths from asthma in children below the age of 15 identified during a two year national study of mortality from asthma in New Zealand.[9]

Methods

Deaths in all age groups, certified as due to or related to asthma, between 1 August 1981 and 31 July 1983 inclusive in people usually resident in New Zealand were investigated.[9] The criterion for inclusion in the study was the use of the words 'asthma', 'asthmatic', or 'asthmaticus' in Part I of the death certificate or on a coroner's report. Cases were identified by monthly regional searches of death certificates and a quarterly search of all certificates at the office of the Registrar General of Births, Deaths, and Marriages. Within four months of death an appropriate family member, the general practitioner, and any specialists consulted were interviewed and hospital records reviewed.

Ethnicity was taken as that stated by the relative interviewed. Data on the ethnicity and age distribution of the population were obtained from the 1981 New Zealand census data.[10]

Questionnaires, interviewers' comments, hospital records, and autopsy data where available were reviewed by two physicians, who assessed the characteristics of the asthma, the quality of care received during the year before death, and, where applicable, the care sought and received in the last episode. They sought to ascertain whether, bearing in mind all the information available, a fatal outcome could have been avoided.

Results

Over the two years 329 deaths were verified as due to asthma;[9] 17 of these were of children aged under 15.

Certification of cause of death. In seven children the general practitioner certified death as due to asthma, and in 10 the coroner reported death as due to asthma. Autopsies were performed on 11 children. One institutionalised child certified as dying of pneumonia, methaemoglobinaemia, and asthma was found on investigation not to have had asthma at the time of death; the word 'asthma' more properly belonged in Part II of the death certificate as an accompanying condition not contributing directly to death, and this child was excluded from study. No cases came to knowledge that were not detected by search of death certificates, and no other children were coded by the National Health Statistics Centre as dying of asthma during the study. One of the 17 children who died from asthma also suffered from cystic fibrosis, and is excluded from the remainder of this report.

Demographic data. New Zealand children belong to three major ethnic groups. Eight European (three girls), one Pacific Island Polynesian boy, and seven Maori (indigenous Polynesian) children (five girls) died of asthma during the two years; the annual mortality rates for these racial groups were 0·59, 1·36, and 3·14 per 100 000, respectively. The deaths in younger age groups were predominantly of Maoris, including all the children aged under 10 who died. The mean age at death of Maori children was 8·6 years (range 2·1–14·8 years) and of European children 12·0 years (range 10·3–14·7 years). Eight of the 16 deaths occurred in the central area of New Zealand's North Island, which has a concentration of Maori people greater than the national average.

Characteristics of asthma and its management (Table). In six cases asthma had developed during the first year of life and in the remainder by the age of 4. Eczema was present in 10 and hay fever without eczema in two. All except one child had a family history of asthma, involving first or second degree relatives. During the year before death asthma was considered by the general practitioner to be improving in five children, unchanged in four, but worsening in seven. Even when at their best in the last year, four were breathless on mild exertion and two breathless even on dressing. Only five children had ever had pulmonary function tests performed by their general practitioner. Of the 14 children aged 8 and over and considered old enough to use peak expiratory flowmeters, 10 had never done so, and only two were using meters regularly at home.

Ten of the 16 children had had two or more emergency visits to their general practitioner or

Table *Patient characteristics and circumstances of death*

Sex	*Age at death (yrs)*	*Race**	*Regular treatment***	*Nebuliser use at home*	*Duration of last attack (h)*	*Place of death*	*Emergency calls in last year*	*Hospital admissions in last year*	*Severity: assessment by general practitioner*
F	2	Maori	—	—	2	Home	0	1	Severe
M	3	Maori	β.Cr	Regular	84	Home	6	1	Severe
F	8	Maori	β.Th.Cr	—	0·5?	Relative's home	Unknown	0	Moderate
F	8	Maori	β.Th.Cr	—	0·2	Relative's home	4	3	Severe
F	10	Maori	β.Th	—	0·1	Car	6	1	Moderate
M	10	Eur	β.Cr.Be	Occasional	16	Home	3	0	Moderate
F	10	Eur	β.Th.Cr.Be	—	0·2	Home	0	0	Moderate
F	11	Maori	β.Th.Cr.Ip	Regular	3·5	Car	5	4	Severe
M	11	PIP	β	—	0·7	Taxi	5	0	Moderate
M	11	Eur	β.Th.Cr	—	14	Home	3	0	Moderate
F	11	Eur	β	—	72	Home	5	0	Mild
M	12	Eur	β.Th.Be.S	Regular	12	Friend's home	10	7	Severe
M	12	Eur	β.Cr.Be.S	Occasional	0·1	Home	4	1	Moderate
M	13	Eur	β	—	0·6	Home	0	0	Mild
F	14	Eur	β.Th.Cr.Ip.S	Regular	10	Home	20	16	Severe
M	14	Maori	β.Be?	—	48	Camp site	0	0	Moderate

*Race: PIP=Pacific Island Polynesian; Eur=European.

**Treatment: β=Beta$_2$ agonist; Th=Theophylline; Cr=Cromoglycate; Be=Beclomethasone; Ip=Ipratropium; S=Oral steroids.

accident and emergency department within the last year. Twelve children had been admitted to hospital with asthma, eight in the year before death. In only five cases was there evidence of a crisis plan for dealing with an asthmatic emergency, the instruction being to contact their doctor, use a nebuliser, or seek direct hospital admission. Four children, however, had never required emergency general practitioner or accident and emergency visits or hospital admissions.

All except one were regularly inhaling a $beta_2$ agonist drug, seven used cromoglycate, seven beclomethasone, and three daily or alternate day corticosteroids. Four children used nebulisers regularly at home for the administration of a $beta_2$ agonist drug, and a further two used a nebuliser occasionally for severe episodes. Only one child using a home nebuliser had a peak flowmeter. Compliance with treatment with drugs was noted by the general practitioner in 14 children of school age as good in seven children, satisfactory in a further two, and poor in five. The specialist reviewing physicians considered that the regular treatment supervised by the general practitioner was inadequate in five cases and that in four cases advice given or follow up arranged by a specialist physician or paediatrician seemed inadequate.

Characteristics of families. Stressful psychosocial circumstances and disturbances of relationships were identified in eight families. Comments made by general practitioners included 'poor family care of children', 'mobile family', 'alcoholic mother', 'neglected child', 'non-compliant family', and 'fatalistic attitude'. In 12 families at least one parent smoked regularly. Two mothers had died of asthma.

Circumstances of fatal episode. Four deaths occurred in January during the summer holiday season. Eight children died after a gradual increase in symptoms of asthma over hours or days. Seven died in less than three hours from the reported onset of their wheezing, and one child was found dead. In only six instances had the general practitioner or his deputy been telephoned. One child died minutes after the doctor was telephoned, two were seen by their doctors and advice was given, but no visit was made in three cases. With one exception, the doctor called was the child's usual practitioner. All children died outside hospital. There was no clustering of times of death; nine of the 16 died between 1800 and 0600 hours.

In two cases excessive treatment with drugs may have contributed to the fatal outcome. A 14 year old child with worsening asthma used a full $beta_2$ agonist inhaler over two days, but used it only three times during the three hours before death. Autopsy revealed severe mucous plugging. An 8 year old child with increasing nocturnal wheeze was given four or five tablets (thought to be sustained release theophylline) over eight hours by a relative, but died from severe asthma. An autopsy was not performed.

Four of the six children with home nebulisers had used these during the last few hours of life when asthma was increasing in severity. Medical advice was obtained by telephone in two of these cases, but other appropriate treatment was not given. Overreliance on a home nebuliser, which was used up to two hourly for 10 and 16 hours, seemed to lead to delay in beginning more aggressive treatment in these two cases. The use of a home nebuliser did not adversely affect management of the other two children. Delays in obtaining help in these were due to failure to appreciate the severity of the attack or reluctance to call for help.

Because of the rapidity of deterioration, the deaths of two children were regarded as unavoidable. A two year old known to have asthma, apparently well apart from an upper respiratory tract infection, was found dead two and a half hours after being put to bed. Autopsy showed mucous plugging of bronchi as well as acute bronchiolitis. A 12 year old with moderately severe asthma well controlled with daily oral steroids and appropriate inhaled drugs died within five minutes of the onset of the attack. His peak expiratory flow rate one and a half hours earlier had been normal, although he then had symptoms of influenza. The physicians classified the deaths of three other children who had precipitous attacks as possibly unavoidable.

In the remaining 11 children avoidable factors contributed to the fatal outcome. In four children long term treatment was inadequate due either to attitudes of the family (one strongly antagonistic to any treatment with drugs, the other accepting asthma with resignation and using minimal treatment) or the medical advisers (two cases). In one instance the family did not call the general practitioner during several hours when asthma was increasing. Difficulties in communication with a general practitioner through a receptionist led to undue delay and death in one case. One child who had recently graduated from a paediatric to an adult respiratory service no longer sought direct hospital admission. She had survived previous severe attacks when admitted directly to hospital. One family delayed calling their general practitioner, then took the child to hospital by car as previous use of an ambulance had resulted in a request for payment. The child died in the car; oxygen might have been life saving. In four cases the response of the medical service and the assessment of asthma seemed inadequate. Advice was given by telephone without the doctor seeing the child, or treatment given was inappropriate to the severity of the asthma. One child was seen by two different locums over three days and on all three occasions received a nebulised beta$_2$ agonist only. No child received additional treatment with steroids before death. No child for whom a doctor was consulted was referred for urgent hospital admission. Two children lived over 20 km from a medical centre, but remoteness from care contributed to only one death.

Discussion

The mortality rate from asthma in New Zealand children is approximately three times that of the United Kingdom.[2] Possible reasons for this include a higher prevalence of asthma, greater severity, or poorer management. There are reports that the prevalence of asthma in New Zealand is higher than that in the United Kingdom.[11-13] Formal comparisons of severity of asthma have yet to be undertaken, but physicians and paediatricians employed in the United Kingdom before coming to New Zealand consistently state that asthma in New Zealand is more severe and less responsive to treatment.[14] That all childhood deaths from asthma in our study occurred outside hospital may reflect a greater severity and a shorter time course of fatal asthma.

The New Zealand study[9] is the first complete national study of mortality from asthma and has identified the largest reported community series of childhood deaths from asthma collected within a short period. We believe our case finding methods detected all childhood deaths from asthma over this period, but as we did not investigate every childhood death, it is possible that mortality from asthma could be even higher. In Avon county, England, 26 of 28 possible cases were detected by a search of death certificates.[4] The present study provides a wider range of deaths than earlier series based on hospital treated patients,[5-8] and more complete information on circumstances surrounding death, including treatment, than was available for cases dying in (37%) or out (63%) of hospital in Avon county.[4]

The dominance of Maoris in the under 10 age group and the fivefold increase in mortality from asthma among Maori children is a cause for particular concern. Prevalence rates for asthma in each ethnic group are not yet known, but differences in prevalence could not be great enough to account for a fivefold higher mortality in Maoris. The numbers of deaths are small and are drawn from a small population of 840 000 in this age group, but the rates are consistent with the data from the much larger adult New Zealand population.[9]

The mean age of European children in our study was 12·0 years, 3·5 years older than in Avon county.[4] Severe asthma is more prevalent in boys both in Britain[4] and in New Zealand,[11] but in neither country is this reflected in the mortality rates. The reason for the apparent 'excess' mortality among girls is not evident.

Medical and family attitudes to treatment with drugs resulted in inadequate treatment in some cases, including instances where inhalers had deliberately not been replaced by a parent so that the child would learn to manage without, and where treatment was said to be unnecessary or inadvisable. Two children subjected to therapeutic nihilism on medical advice had within the month before their death been started on treatment with inhaled beta$_2$ agonist for severe asthma because of worsening symptoms, but had not been given other drugs, including treatment with steroids. In only two cases did we find evidence of apparently excessive drug use. Overreliance on a home nebuliser for administering bronchodilator drugs resulted in delay in beginning more adequate treatment in two other cases. It is of great concern that no child had been given additional treatment with steroids during the fatal attack. By contrast, six of 13 children in Avon county whose treatment was recorded were given steroids, although the dose was inadequate in four.

The disturbed family circumstances encountered in half of these children may have contributed to mortality. Neglect of children, care of children by other than immediate family members, and stressful home circumstances with ill or alcoholic parents seemed relevant. These family circumstances probably led to less attention being given to the child's asthma.

Assessment of severity of asthma can be difficult, but in many of these cases the assessments made by the families and their doctors seemed inadequate. The virtual absence of peak flow monitoring must have contributed to this lack of awareness of severity.

Four of the fourteen children aged 5–14 years died in January during the New Zealand summer. Exposure to allergen might possibly have been associated with increased mortality. Seasonal variation in childhood asthma admissions and deaths has recently been reported in the United Kingdom;[15 16] heightened bronchial reactivity associated with spring pollens was suggested as a possible cause of summer deaths. Unlike the findings in New Zealand[9] and British[7] adults, and in those children in Avon county for whom time of death was known,[4] there was no excess in nocturnal deaths in

New Zealand children, despite 14 of the 16 having more troublesome symptoms in the evenings or through the night.

Many of the factors associated with mortality from asthma in childhood were similar to those found in the British Thoracic Association study of mortality among adults with asthma[17]—namely, chronic undertreatment, lack of objective assessment of severity, and delay in calling help. Disturbed family circumstances may compound these problems in childhood where clearly parental care and knowledge are of greater importance.

At least 11 of the 16 deaths in children aged under 15 were associated with avoidable factors. Measures that we believe could lower the mortality rate from asthma among children include increased family awareness of asthma and understanding of a crisis plan for dealing with an emergency due to asthma; regular assessment of severity and control with peak flow monitoring; improved access of high risk children with asthma to medical care, including provision for direct hospital admission; and removal of financial barriers, including the cost of ambulances, general practitioner consultations, and peak flowmeters. Improved long term care, including education to accept regular treatment to control abnormal lung function as well as symptoms, may reduce mortality. While further studies are required to prove the benefits of both education and long term treatment this survey of childhood deaths from asthma suggests these are areas for particular action.

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How to use a rotahaler

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SUMMARY The bronchodilator response after five different modes of salbutamol inhalation by rotahaler was assessed in 15 asthmatic children in a double blind cross over study. Inspiratory flow rates lower than 50 litres/minute were associated with a significant reduction in response compared with flow rates higher than 60 litres/minute, but tilting the head back during inhalation and holding the breath for 10 seconds had no significant effect on bronchodilation. Peak inspiratory flow rates measured in 150 normal children and 13 asthmatic children with acute wheeze showed that many young children and many children with severe bronchoconstriction were unable to generate a sufficiently high inspiratory flow rate to obtain maximum benefit from rotahaler treatment. Children using a rotahaler should be taught to inhale as quickly as possible and not with a quiet deep breath as recommended in the instruction leaflets.

The rotahaler was designed to make inhaled medication more convenient and effective for asthmatic patients. Improving the success of this treatment, however, is not only a matter of inhaler design but also of optimising and simplifying instructions and the mode of inhalation. There is, at present, considerable doubt about the best technique for using the rotahaler in asthmatic children. The instruction leaflets provide some guidance on the correct manner of use, but the basis of these instructions has not been confirmed in controlled clinical trials.

We conducted a series of studies in asthmatic children to elucidate the optimum rate of inhalation, the importance of tilting the head back during inhalation, and the importance of holding the breath afterwards. Furthermore, we have studied the maximum inspiratory flow rates that can normally be generated through the rotahaler in both normal and asthmatic children.

Patients and methods

Study 1—modes of inhalation. Eleven boys and four girls aged 7 to 14 years (mean 11 years) participated in the study. All suffered from chronic or episodic wheeze associated with an increase in forced expiratory volume in one second (FEV$_1$) of at least 15% after one puff of terbutaline. They received regular inhaled treatment with corticosteroids and beta$_2$ stimulants. The study was approved by the ethical committee of Northern Jutland, and informed consent was obtained from all children and their parents.

The children were studied on six separate occasions at the same time of day. Before each visit, treatment with inhaled corticosteroids and beta$_2$ agonists was stopped for 48 and 12 hours respectively. A study on each child was only performed if the baseline FEV$_1$ was within 15% of its value on the first study day, and if this was not the case the child was asked to make a further visit on another day.

The patients inhaled through a rotahaler in series with a pneumotachygraph. One capsule of placebo or 0·2 mg salbutamol was given on each study day and the children wore a nose clip during inhalation. The differential pressure signal from the pneumotachygraph (proportional to the flow rate of inspired air) was fed to a pressure transducer, from which the analoque signal was integrated to give the inhaled volume. Throughout the inhalation the children could see the variation with time of both inspiratory flow rate and inhaled volume on the screen of an oscilloscope. This was used as a teaching aid so that all children, after some practising in the morning, were able to make reproducible, standardised inhalations at a fixed inspiratory flow rate. Inspiratory flow rates and volume were recorded for analysis.

During treatment the children inhaled as deeply as possible from residual volume. They repeated the inhalation until the capsule was emptied. The capsule was always inserted into the rotahaler and split by an adult.

The design was that of a controlled double blind, double dummy cross over study. During the first four study days the children were treated with *placebo* (A), salbutamol inhaled at 30 to 50 l/minute (*slow*=B), salbutamol inhaled at 60 to 80 l/minute (*medium*=C), and salbutamol inhaled at 90 to 120 l/minute (*fast*=D) in a randomised cross over fashion. During these days the head was tilted back during inhalation which was followed by breath holding for 10 seconds. When the results from the first four days had been analysed the children participated for another two days of fast inhalation, one day without a breath holding pause (E) and one day without tilting the head back during the inhalations (F) (randomised sequence).

Pulmonary function was measured before, and at 30 and 90 minutes after each treatment. The measurements were performed in a body box and the bronchodilator response was assessed by measuring changes in FEV$_1$, forced vital capacity, residual volume, and specific airways conductance. Both absolute values and the percentage of the predicted value were evaluated. The best of three measurements was studied.

Study 2—peak inspiratory flow rates in normal children. To evaluate the maximum inspiratory flow rates that various age groups of children can generate through the rotahaler, 159 children aged between 3½ and 15 years were taught to inhale as quickly as possible through a loaded rotahaler in series with the pneumotachygraph. The flow and volume *v* time curves were recorded and the best of three measurements was analysed. In addition, peak expiratory flow rate was measured on a Mini Wright peak flow meter, and FEV$_1$ and forced vital capacity on a dry wedge spirometer (Vitalograph) (best out of three). These measurements were done in all children in a kindergarten and a small public school who were able to cooperate (nine were unable to).

Study 3—acute asthma. Thirteen asthmatic children aged between 6 and 12 years (mean=8·9 years) were studied as described in study 2 during an episode of acute wheeze and again after their pulmonary function had improved.

Statistics. Friedman's test was used to evaluate any overall difference between treatments. If significant effects for treatment or time were found the results were analysed by parametric and non-parametric methods (paired *t* tests and Wilcoxon's rank sum test). As these results were similar, however, only the results of the *t* tests are given. Values given in the text are mean (SEM).

Results

Modes of inhalation. The FEV$_1$ as a percentage of the predicted value before and after use of the rotahaler on the six days of treatment is shown in Fig. 1. There was no statistically significant difference between the initial FEV$_1$ on the six days of treatment. The FEV$_1$ before treatment varied from 47% to 72% (mean 59·7%) of the predicted value.

All active treatments resulted in a significant increase in FEV$_1$ compared with placebo. The improvement after medium and fast inhalations was significantly greater than that after slow inhalations ($P<0{\cdot}01$). There was no difference between the response to medium and fast inhalations with the head tilted back and a breath holding pause of 10 seconds. At fast inhalation rates neither tilting the head back nor holding the breath influenced the bronchodilator effect.

On the whole the results were similar for forced vital capacity and specific airways conductance. For residual volume the difference between slow inhalations and the various other active treatments failed to reach statistical significance.

Mean peak inspiratory flow rate was 43 (range 36 to 50) litres/minute on the slow day, 69 (range 60 to 80) litres/minute on the medium day and 108 (range 71 to 130) litres/minute on the fast day (the two youngest children were unable to generate flows above 90 litres/minute). There was no significant difference in the flow rates between the three fast days (D, E, and F), nor was there any difference between the mean inhaled volume on the six days (this varied from 2·32 to 2·40 litres).

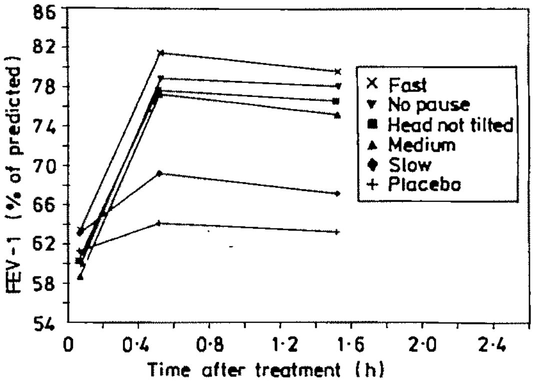

Fig. 1 *Mean forced expiratory volume in one second as a percentage of the predicted value after various modes of inhaling 0·2 mg salbutamol or placebo from a rotahaler (see text).*

Peak inspiratory flow rates of normal children. Peak inspiratory flow rate varied significantly with age ($r=0\cdot83$; $P<0\cdot01$) and with peak expiratory flow ($r=0\cdot90$; $P<0\cdot01$) (Figs. 2 and 3). In addition, inhaled volume was found to correlate significantly with forced vital capacity ($r=0\cdot79$; $P<0\cdot01$).

Acute asthma. The mean peak inspiratory flow rate measured during acute attacks of bronchoconstriction, when mean peak expiratory flow was 102 litres/minute, was significantly lower than the mean peak inspiratory flow rate measured after recovery, when mean peak expiratory flow had increased to 247 litres/minute ($P<0\cdot01$) (Fig. 4). During acute wheeze, nine children had inspiratory flow rates below 50 litres/minute.

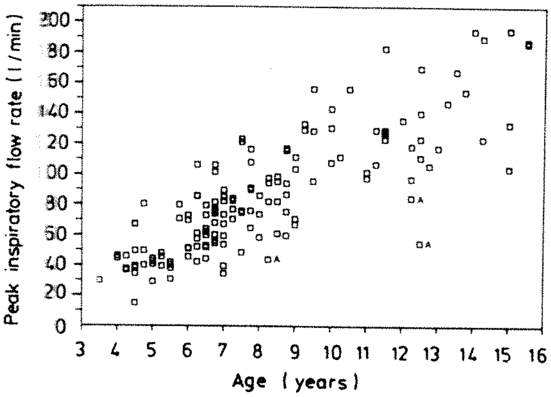

Fig. 2 *Peak inspiratory flow rate through a rotahaler in various age groups of children (A = a child who was found to suffer from asthma during the study).*

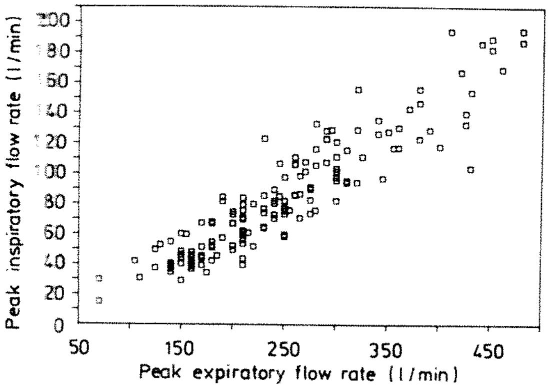

Fig. 3 *Variation in peak inspiratory flow rate through a rotahaler and peak expiratory flow rate in 150 children.*

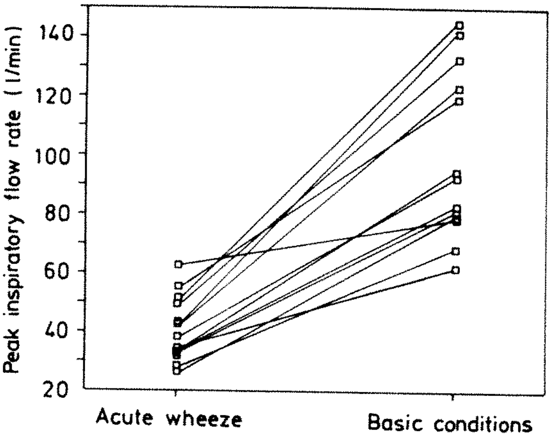

Fig. 4 *Peak inspiratory flow rate through a rotahaler in 13 asthmatic children during an episode of acute wheeze and after recovery.*

Discussion

The instruction leaflets accompanying the rotahaler recommend a quiet deep inhalation. This may be best for adults and older children but the peak inspiratory flow rates that the children in the various age groups in the present study were able to generate through the rotahaler and the finding of a reduced effect at low inspiratory flows, indicate that such advice will result in reduced bronchodilation in many children. Furthermore, the study showed that tilting the head back during inhalation, and breath holding afterwards can be safely omitted from the instructions. This would facilitate teaching and perhaps improve compliance.

The lack of benefit from holding the breath after inhalation has also been shown in some studies in adults using pressurised aerosols,[1] but this finding does not agree with those of Newman.[2] Newman, however, only found a beneficial effect of breath holding at very low inspiratory flow rates (25 litres/minute). To our knowledge the importance of tilting the head back during inhalation so that the particles may follow a straighter path to the trachea has not previously been investigated under controlled conditions, nor has the importance of breath holding been studied in patients using a rotahaler.

The correlation between inspiratory and expiratory pulmonary function measurements agrees with the clinical observation that many asthmatics complain not only of expiratory but also of inspiratory difficulties during episodes of wheeze. This has some important clinical implications, since it means that younger children who can normally use a rotahaler efficiently, may not be able to gain full benefit during attacks of acute bronchoconstriction or in periods of bad control of symptoms. In these cases it may be necessary to increase the inhaled dose or to use other ways of drug delivery. These suggestions are supported by the results of a recent clinical trial.[3]

Our finding that the bronchodilator response was reduced at slow inspiratory flow rates is quite opposite to that in adults using pressurised aerosols,[2 4] and emphasises doubts about the validity of extrapolating results from one inhaler to another. We do not know the exact cause of the reduced effect. It has been shown in vitro, however, that the drug/lactose powder mix in the capsules requires a certain amount of inspiration energy to break up the agglomerates into sufficiently small particles (personal communication from Glaxo), and it is possible that the reduced effect after slow inhalations was due to insufficient breaking up of the large drug/lactose particles.

Studies with pressurised aerosols and teflon particles have shown that high inspiratory flow rates may increase the likelihood of a more central deposition of drug in the lungs.[2 5 6] There has been no direct study of the rotahaler comparing pulmonary deposition at different rates of inhalation. We think that the theoretical advantage of medium rate inspiration is easily outweighed by the difficulties of administering this regimen in children because of the variation in inspiratory flow rate with age and day to day differences in pulmonary function. We therefore suggest that fast inhalations should be recommended for children using a rotahaler until controlled clinical studies of the day to day management of ambulatory asthmatics have proved otherwise.

Conclusion

Children should be taught to inhale as quickly as possible through their rotahaler. They need not tilt their head back during the inhalation or hold their breath afterwards. During episodes of wheeze young children may gain less benefit from rotahaler treatment because they cannot generate sufficiently high inspiratory flow rates.

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An article by Reiser and Warner on inhalation treatment for asthma appears in the Personal practice section of this issue.

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Oral corticosteroids for wheezing attacks under 18 months

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SUMMARY In a double blind, partial crossover trial we compared treatment with prednisolone with treatment with placebo (56 treatments) in 38 children aged less than 18 months (mean age 9·8 months, range 3–17 months), 30 of whom had required previous admission to hospital. Placebo or oral prednisolone 2 mg/kg/day in two divided doses for five days was given during acute exacerbations of symptoms on an outpatient basis. Daily symptom scores of cough, wheeze, and breathlessness did not show any significant difference in rate of improvement or overall outcome, either between the two whole groups or within subgroups aged less than 6 months, 6–12 months, and 12–18 months. Parental preference failed to indicate superiority of treatment with prednisolone over treatment with placebo in the 18 crossover patients, and parents were equally as likely to feel that treatment with either placebo or prednisolone had had positive effect in non-crossover patients. Two children required admission to hospital during treatment, one aged 5½ months being treated with prednisolone, and one aged 14 months being treated with placebo.

Recurrent wheezing attacks in children aged under 18 months are a considerable source of morbidity and a not uncommon cause for admission to hospital. Although the list of differential diagnoses is lengthy and includes conditions such as cystic fibrosis, aspiration syndrome, and foreign body, most of these children are suffering from asthma. The clear benefit to the patient after appropriate treatment with anti-asthma drugs consequent on correct diagnostic labelling has been shown by Speight *et al.*[1] Sadly, this does not necessarily hold true for very young children due to their variable and often non-existent responsiveness to treatment with bronchodilators.[2] Although the mechanisms underlying this limited responsiveness are by no means fully understood, one of the suggestions has been that the pathology is primarily that of inflammation, with mucosal oedema and inflammatory exudate being principal features, none of which would be susceptible to specific bronchodilators. This fact, coupled with the extreme paucity of published information on the role of corticosteroids in the age group 0–18 months, prompted us to assess what part corticosteroids might have to play in the management of this difficult clinical problem.

Patients and methods

Thirty eight children aged less than 18 months were studied. There were 28 boys and 10 girls. All had suffered at least two previous attacks of wheezing, and in none was any diagnosis other than asthma under active consideration. In an attempt to avoid treating trivial and rapidly self limiting episodes only those attacks that had lasted at least 48 hours and were still of sufficient severity to merit therapeutic intervention on standard clinical criteria were included. Minimum requirements were persistent wheezing and/or coughing, associated with tachypnoea, subcostal recession, and rhonchi on examination, these symptoms being sufficiently troublesome to cause some disturbance to feeding and sleeping. Any child requiring immediate admission to hospital was excluded. Patients were enrolled into the study after self referral to our unit by the parents, initial contact having been made in the outpatient department or during a previous hospital admission for asthma.

Patients were randomly allocated to treatment with either placebo or soluble prednisolone 1·0 mg/kg twice daily for five days on a double blind basis. Crossover was completed either if a child had showed no improvement eight days after beginning treatment—that is, three days after finishing treatment—or if they presented with a subsequent attack at a later date. If treatments, such as bronchodilator or antibiotics had already been begun by the general practitioner they were continued.

Parents were asked to maintain a diary record at home during the course of treatment and for the subsequent three days. Scores of 0 to 3 (0=no symptoms, 1='a bit', 2='quite bad', 3='very bad') were recorded for each of cough, wheeze, and breathlessness/difficulty in breathing for both day and night, giving a possible maximum total for each 24 hours of 18. Patients were reviewed at eight days, and at that time parents were asked whether or not they considered that the treatment had in any way altered the course of the attack compared with previous similar (untreated) attacks.

Statistical analysis employed the χ^2 test, Fisher's exact test, and Mann-Whitney U test where appropriate. Statistical validity of the results was estimated using the sample size and power estimations described by Fleiss.[3]

Informed consent was obtained from the parents before entry into the trial. The study was approved by the local ethical committee.

Results

Thirty eight children were given a total of 56 treatment courses (18 crossover patients), 29 prednisolone and 27 placebo. There were no significant differences between the groups with respect to age, sex, age at onset of first symptoms, number of previous admissions to hospital for asthma, or length of attack before starting treatment (Table 1).

Table 1 *Patient details (no of patients=38; no of treatment courses=56)*

		Group treated with prednisolone (n=29)	*Group treated with placebo (n=27)*
Age at study	(mean (SD)	10·4 (4·1)	9·3 (3·7)
(months)	range)	3·5–17	3·2–15·7
Sex	(M:F)	19:10	21:6
Age at onset	(mean (SD)	3·5 (3·1)	3·4 (2·7)
(months)	range)	0–12	0–11
Previous admissions:			
No (%) of patients ≥1		21 (72%)	21 (78%)
No of admissions		30	34
Length of attack			
before treatment	(mean (SD)	8·0 (5·6)	7·3 (5·8)
(days)	range)	2–21	2–21

There were also no differences in personal history of eczema or family history of asthma, eczema, or hay fever. Three of the group given prednisolone had been prescribed bronchodilators by their general practitioner at the onset of the attack compared with five in the group given placebo; a further two in the group given placebo had been given antibiotics.

The severity of the attacks was similar in the two groups at the time of beginning treatment, there being no difference in scores on day 1 (median of group given prednisolone=9, median of group given placebo=9·5; p=0·64 by Mann-Whitney test). Neither was there any difference between the groups' scores on days 3, 5, and 7 (Table 2), however, suggesting similar progress through and outcome of the courses of treatment.

Figures 1–3 present data from all the patients studied. Analysis of these data by comparing the number of positive and negative changes over the intervals day 1 to day 3, day 1 to day 5, and day 1 to day 7 showed no significant difference between treatment with prednisolone and placebo in the

Table 2 *Median values of symptom score on days 1, 3, 5, and 7*

Patients' age group	*Treatment*	*Median score*			
		Day 1	*Day 3*	*Day 5*	*Day 7*
0–18 months (n=38)	Prednisolone (n=29)	9	8	7	5
	Placebo (n=26)†	9·5	9	5·5	6
0–6 months (n=10)*	Prednisolone (n=6)	8·5	9·5	9	7
	Placebo (n=6)	8	11·5	9	10
6–12 months (n=17)*	Prednisolone (n=13)	9	8	5	4
	Placebo (n=14)	9·5	8·5	4	3·5
12–18 months (n=11)	Prednisolone (n=10)	10	8	6·5	4·5
	Placebo (n=6)†	11·5	10·5	7	5

No significant difference at 5% level between treatments (Mann-Whitney test).
*One patient had progressed to next age subgroup at the time of crossover treatment.
†One scoresheet lost by parents.

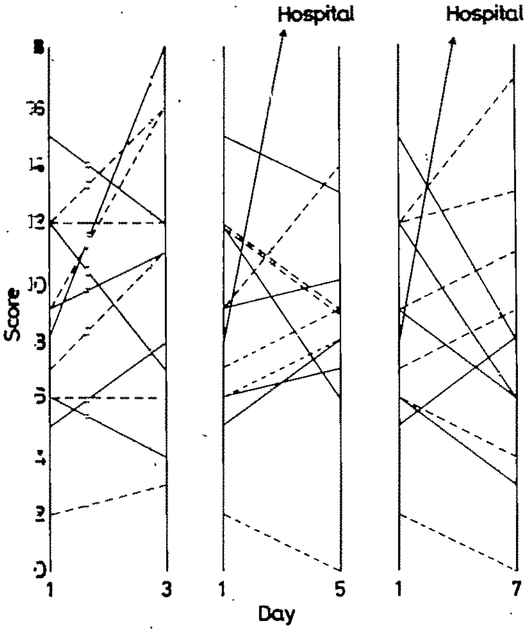

Fig. 1 *Progress of individual patients, 0–6 months (——=prednisolone; – – – –=placebo).*

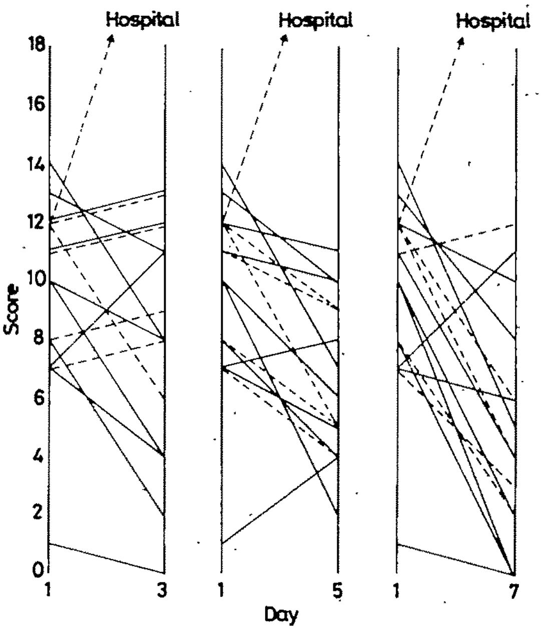

Fig. 3 *Progress of individual patients, 12–18 months (one placebo not shown—'no difference whatsoever'; ——=prednisolone; – – – –=placebo).*

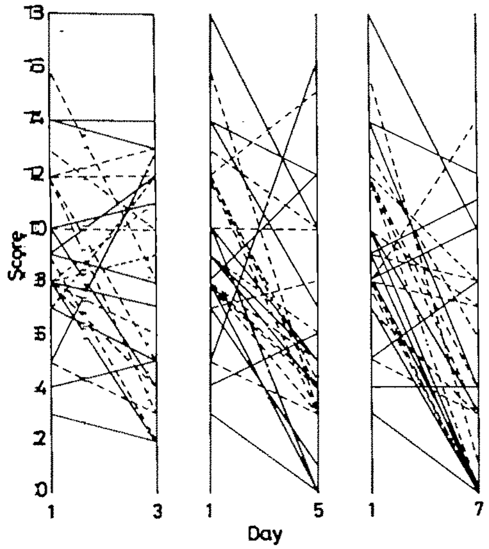

Fig. 2 *Progress of individual patients, 6–12 months (——=prednisolone; – – – –=placebo).*

whole study or within any of the age subgroups. There was, however, a trend to greater efficacy of treatment with prednisolone in the day 1–3 period (17/29 (59%) of the group given prednisolone improved *v* 9/27 (33%) of the group given placebo improved; $\chi^2=2\cdot65$, $p<0\cdot1$), this trend being most pronounced for the 12–18 month age subgroup (7/10 (70%) of the group given prednisolone improved *v* 1/6 (17%) of the group given placebo improved; $p=0\cdot058$ by Fisher's exact test). Analysis of the median change in score over the same intervals showed no significant overall difference between the two treatments, with the trend towards earlier resolution of symptoms on treatment with prednisolone over the day 1–3 interval being less apparent (group given prednisolone median score change −1 *v* group given placebo median score change +0·5; $p=0\cdot54$ by Mann-Whitney test).

Parents were unable to identify positive benefit from treatment with prednisolone over treatment with placebo. In the complete treatment groups 16 out of 29 courses of prednisolone were thought not to have benefited the child, although 12 were thought to have done so; 10 were positive and 17 were negative for placebo. Again, there was a trend towards perceived greater efficacy of treatment with prednisolone in the 12–18 month age group (5/9 of the group given prednisolone benefited (one 'didn't know') *v* 1/7 of the group given placebo benefited), but this too failed to reach significance.

If we limit our analysis to only those 18 patients who completed a full crossover trial (36 treatment courses), the two treatment groups are even less dissimilar and the trend towards earlier improvement in the older age group is lost.

In a largely negative and small clinical study it is important to make an estimate of its power. Given that the proportions of placebo courses that produced improvement over the day 1–3 period were 33% and 17% for the whole group and the 12–18 month age subgroup, respectively, it would seem reasonable to aim for an improvement rate of three out of four (75%) for treatment with prednisolone as indicative of a clinically acceptable benefit—this study had a 92% chance of revealing this likelihood of benefit for the whole group and an 89% chance for the 12–18 month age subgroup. The higher proportion of children who improved on treatment with placebo over the longer period of five or seven days gives the study about a 50% chance of picking up what could only be small differences over these intervals.

Two children required admission to hospital during a treatment course—one 5½ month old boy on the fourth day of treatment with prednisolone and one boy of 14 months on the third day of treatment with placebo.

There were no side effects reported by the parents and none was detected on clinical examination at the time of review three days after completing the five day course of treatment.

Discussion

We have been unable to show consistent benefit from treatment with corticosteroids over and above treatment with placebo for moderately severe asthma attacks in children aged under 18 months.

Could it be that our method is too insensitive? Different observers (in this case different sets of parents) are bound to assess the severity of symptoms on differing scales, not least because they can only relate to the previous range of severity experienced by the individual child under observation. Therefore, to analyse total daily scores as though uniformly representative of a single scale of severity could mask minor, and possibly even quite large, differences between the groups; we were not altogether surprised to find no difference in group scores on days 1–7.

This difficulty is to a certain extent overcome by analysing the change in score between two given days (improvement *v* no improvement) for each patient, as each statistic is then self controlled and intersubject variability is no longer a problem. With this method we are still unable to separate the progress and outcome of the two different treatment courses to a significant degree, even when restricting our analysis only to the 18 crossover patients. Our third approach was to seek parental opinion about whether or not the treatment had affected the course of the attack, a valid assessment given that most of these parents would have witnessed many similar previous attacks. Not only might they be able to report overall outcome in terms of 'dramatic improvement' or 'no change'/'deterioration', but it was also hoped that they might detect more subtle effects such as 'got better quicker than usual'—this point, though clearly very subjective, being an important possible benefit from treatment and one unlikely to be recognised by analysis of daily scores alone. Parents were just as likely, however, to feel that treatment with placebo had benefited the child as treatment with prednisolone. More importantly, over half the children that were given prednisolone were thought not to have been helped.

We do not consider that we were treating illness so trivial that we might miss a steroid response even if it were present. As a group these 38 children had suffered considerable morbidity in the past, with 30 (79%) of them having had previous admissions to hospital with asthma. Moreover, at the time of starting treatment they had been unwell for a mean of seven to eight days and were still constitutionally upset by their symptoms. Nor do we feel that we simply undertreated with prednisolone—there are no published data on minimum dosage, but prednisolone 2 mg/kg/day for five days seems more than adequate in clinical practice with older children under similar circumstances, and there is evidence that massive doses confer no added advantage in severe attacks.[4]

Our small study is statistically powerful enough to have been able to pick up a theoretical improvement rate of three out of four cases after three days' treatment with prednisolone, but our results fall short of this arbitrary but desirable aim. The tendency of asthma attacks to improve over a longer period is such that this study would only have a 50% chance of identifying a small but significant advantage of treatment with prednisolone over five to seven days if it were to exist. It is pertinent, however, to note that two days after completing a five day course of treatment with prednisolone (scores on day seven) 11 out of 29 cases were still quite unwell with scores of eight or more.

Although it is almost universal practice to administer corticosteroids to patients with either chronic persistent or acute asthma, there is still very little documented proof of efficacy. Grant argued strongly in favour of the use of steroids in acute severe asthma in adults,[5] though Luksza disputed this view.[6] There is objective evidence of improvement in lung function in acute asthma in adults after infusion of hydrocortisone;[7] similarly, administration of both intravenous[8] and oral[9] prednisolone have been shown to increase lung function in chronic asthma in adults. The few studies in children are inconclusive. Pierson *et al* have shown significant improvement in arterial hypoxaemia, independent of changes in ventilatory function, after intravenous infusion of betamethasone, hydrocortisone, or dexamethasone during status asthmaticus,[10] but Kattan *et al* could show no benefit from intravenous hydrocortisone over and above bronchodilator in a similar group of children.[11] Tal *et al* studied the effects of dexamethasone, salbutamol, and placebo, singly or in combination, on a group of wheezing infants in hospital.[12] They concluded that the effects of placebo, salbutamol alone, and dexamethasone alone were essentially the same, but that salbutamol and dexamethasone together were additive and significantly better than either alone. Their numbers in each treatment group, however, were very small and included some children with an attack of acute bronchiolitis, a condition well documented as being unaffected by treatment with corticosteroids.[13 14] Despite these reservations about their study, we would agree with their findings suggesting that corticosteroids alone do not confer great advantage in the treatment of this age group as a whole, although we cannot state categorically that treatment with prednisolone did not improve some individuals. We are unable to predict which individuals these might be—of those whose parents thought that treatment with prednisolone had helped, there was no variable among age, sex, family history, length of attack, or initial severity score that differentiated them from 'non-responders'.

In conclusion, we have been unable to show definite clinical response attributable to treatment with oral prednisolone in moderately severe asthma in children aged under 18 months. We cannot extrapolate from our data to comment on what effect corticosteroids might have in the treatment of acute severe life threatening asthma in this age group.

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Bacterial infection and atopic eczema

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SUMMARY One hundred and ninety children with atopic eczema were studied prospectively for two and a half years. The mean period of observation was 13 months. Seventy six children (40%) had between them 164 episodes of exacerbation of eczema due to bacterial infection, and in 52 (32%) infection recurred within three months of a previous infection. Twenty five episodes (15%) led to admission to hospital. *Staphylococcus aureus* was recovered in 97% of episodes, in combination with β haemolytic streptococci in 62%. Physical signs suggesting infection were pustules, crusting, and a weeping discharge, but these signs alone are not diagnostic, and an exacerbation was only attributed to infection if there was a response to anti-infective treatment. Exacerbation of atopic eczema due to bacterial infection is common, the physical signs of infection are not always clear, and there is a case for a trial of oral antibiotics in any child with troublesome atopic eczema.

There is a high rate of skin colonisation with *Staphylococcus aureus* in atopic eczema. For example, Leyden *et al*[1] recovered *S aureus* not only from more than 90% of isolates taken from chronic eczematous lesions, but also from approximately 70% of isolates taken from unaffected areas of the skin. By contrast, Noble[2] found *S aureus* on the skin in fewer than 5% of isolates taken from various sites in 382 normal children. The high frequency of *S aureus* carriage in clinically normal skin in patients with atopic eczema may be contamination due to continual dispersion from skin lesions or colonisation. Impaired neutrophil chemotaxis,[3] and greater adherence of *S aureus* to keratinised epithelial cells of atopics[4] may contribute to the high rate of skin colonisation.

It is often held that while the skin in atopic eczema is usually colonised with *S aureus*, bacterial skin infections are uncommon, and less frequent than might be expected in a disease characterised by scratching and excoriation.[5] Observation of children with atopic eczema suggests, however, that in this disorder the frequency of bacterial skin infection is higher than previously suspected. This report describes a prospective study of bacterial infections in children with atopic eczema.

Patients and methods

Between January 1982 and July 1984, all children with atopic eczema referred to the Department of Child Health at Booth Hall Children's Hospital were studied prospectively for evidence of skin infection. One hundred and ninety patients, aged 7 weeks to 17 years (median 3 years) were observed for 2480 patient months, with a mean of 13 months.

The presence of pustules, a purulent discharge, crusting combined with weeping (Figure (a)), crusting alone (Figure (b)), or sudden appearance of weeping, were taken as physical signs of infection. Children were seen as outpatients at intervals no longer than three months, and their parents were asked to bring the child if there was sudden or unexpected deterioration of the eczema or if any of the above signs were noticed. Episodes of infection due to Herpes simplex,[6] Herpes zoster, and Coxsackie A have been excluded. Nine episodes of infection treated by the general practitioner and not seen at hospital were also excluded.

The criteria for 'infection' comprised (a) one of the above signs, together with (b) response to oral antibiotic or topical antiseptic treatment (see below). Episodes that did not respond to this treatment were classified as 'possible infections'. A recurrent infection was defined as one occurring within three months of a previous infection.

The following oral antibiotics were given in a dosage of: (a) phenoxymethylpenicillin, flucloxacillin, fusidic acid, or erythromycin—under 10 years 125 mg four times daily; over 10 years 250 mg four times daily: (b) cefadroxil: under 5 years 250 mg twice daily; over 5 years 500 mg twice daily.

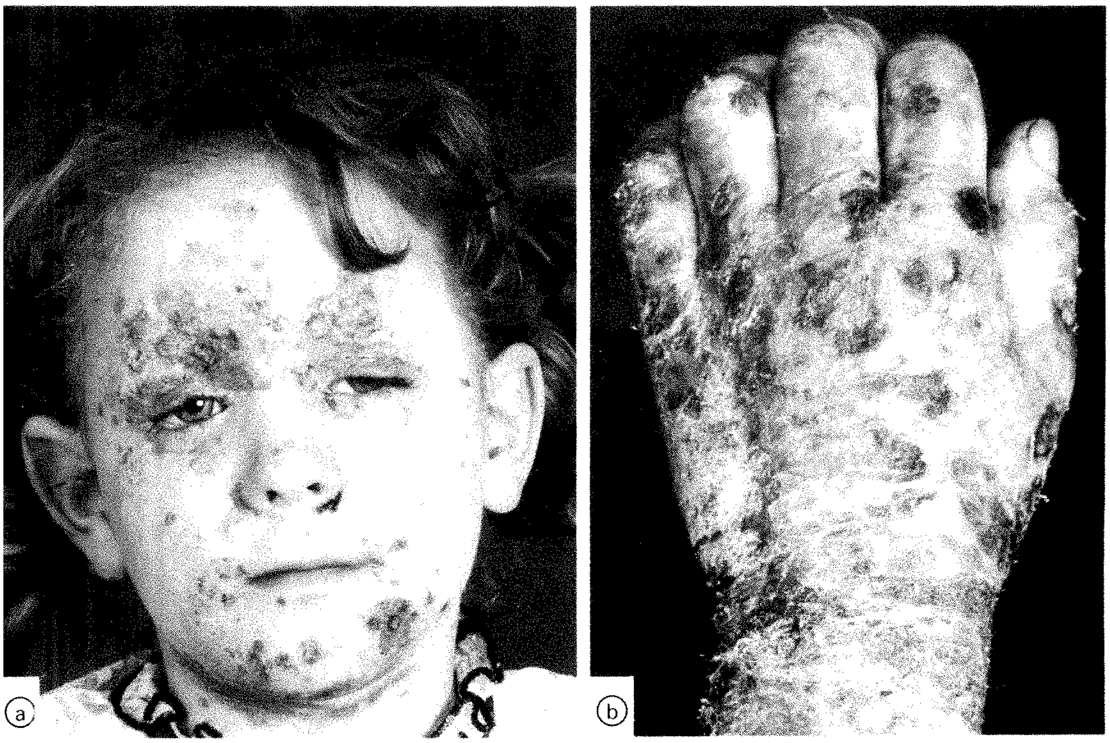

Figure *A 6 year old child with atopic eczema. The crusting plus weeping on the face (a), and the dense crusting on the hand (b), suggest the presence of bacterial infection.*

Antibiotics were always given in tablet or capsule form because of the possibility of adverse reaction to colouring agents or preservatives present in liquid preparations. A combination of phenoxymethylpenicillin plus flucloxacillin was the first choice for oral antibiotic treatment. Either antibiotic was used alone only for recurrent infections where eradication of a single organism was intended. Cefadroxil was used in cases where it was suspected that the family would not comply with four times daily dosage of two antibiotics. Erythromycin or fusidic acid were used in cases of penicillin allergy. A combined topical corticosteroid-antiseptic ointment was used in the presence of chronic lichenified patches of eczema. Topical treatment with an antiseptic, povidone-iodine 10% ointment, was used where a purulent discharge was present. Topical treatment alone was given only where it seemed that the infection was localised.

Results

One hundred and sixty four episodes of infection and 20 episodes of possible infection (as defined above) occurred in 76 (40%) of the 190 patients. Twenty six patients were infected at their first visit. Twenty five episodes (15%) of infection led to admission to hospital. Three children were admitted twice for this reason. Twenty three admissions were because of the severity and extent of the infected lesions, and two admissions were because of systemic illness associated with the infection. The bacteriological results and details of treatment are given in the Table.

Recurrent infections. Fifty two (32%) of the 164 infections were recurrences within three months of a previous infection, 30 of the 52 occurring within one month of the previous infection. Attempts to prevent further recurrences comprised the topical application to the inside of the nostrils (four times daily for two weeks) of chlorhexidine hydrochloride 0·1% and neomycin sulphate 0·5% cream (21 infections), and the addition of 25 ml of chlorhexidine gluconate 1·5% and cetrimide 15% solution to each bath. There are insufficient data to assess the efficacy of either procedure.

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Table *Infections and possible infections: bacteriology results and treatment*

	Infections (n=164)	%	*Possible infections (n=20)*	%
Bacteriology				
Skin swab results	*Staphylococcus aureus* + β haemolytic streptococci	62*†	*S aureus* + β haemolytic streptococci	62
	S aureus alone	35*	*S aureus* alone	38
	β haemolytic streptococci alone	3		
Lancefield grouping of β haemolytic streptococci	Group A	68‡	Group A	100
	Group B	13		
	Group C	8		
	Group G	10		
	Group L	1		
Resistance of *S aureus*	Penicillin	70	Penicillin	100
	Erythromycin	18		
	Tetracycline	12		
	Fusidic acid	1		
	Gentamicin	1		
Treatment				
Oral antibiotics for 14 days		94		81
	Phenoxymethylpenicillin + flucoxacillin	63	Phenoxymethylpenicillin + flucoxacillin	82
	Flucoxacillin	14	Flucoxacillin	6
	Cefadroxil	8	Phenoxymethylpenicillin	6
	Phenoxymethylpenicillin	6	Phenoxymethylpenicillin + fusidic acid	6
	Fusidic acid + erythromycin	3		
	Fusidic acid	3		
	Erythromycin	3		
Topical steroid/antiseptic		33		40
	Clioquinol 3%/hydrocortisone 1% ointment	25	Clioquinol 3%/hydrocortisone 1% ointment	40
	Chlorquinaldol 3%/hydrocortisone 17-butyrate 0·1% oint.	6		
	Clioquinol 3%/flurandrenolone 0·0125% ointment	2		
Topical antiseptic	Povidone-iodine ointment	21	Povidone-iodine ointment	5

*Combined with pneumococcus in one patient.
†Combined with *Pseudomonas aeruginosa* in one patient.
‡7% were resistant to erythromycin.

Nose and throat swabs. *Staphylococcus aureus* was recovered from 41% of all nose swabs. Beta haemolytic streptococci were recovered from 24% of all throat swabs and from 42% of those from patients with positive streptococcal cultures from the skin. In no patient did a nose swab indicate a staphylococcus when one was not also found in the patient's skin. In three patients who had only a staphylococcus in the skin, a throat swab detected β haemolytic streptococcus, and in two of these three this was a group C organism.

Adverse effects. Deterioration of the eczema was attributed to an oral penicillin in two patients, and the treatment changed to another antibiotic. The combination of two penicillins resulted in diarrhoea in two patients, causing the parents to stop treatment. The unpleasant taste of flucloxacillin powder led to a change to the antibiotic syrup in two patients. The antiseptic component of the topical antiseptic-corticosteroid combinations invariably caused yellow staining of clothes or hair.

Discussion

There are problems with the definition of 'infected eczema'.[7] While the discharge of pus strongly suggests infection,[8] other appearances are not so clearly diagnostic. The presence of weeping is unreliable; although it may be due to infection, it may also be the result of a deterioration due to allergy or simply to incessant scratching. The presence of bacteria on eczematous skin is almost universal,[9,10] and colonisation cannot be considered a criterion of infection. In this study, the definition of infection included response to anti-infective treatment, usually oral antibiotics. Oral antibiotics were chosen because of the widespread nature of many of the infections, and the severity of some. Topical antibiotics were not used because of the possibility of sensitisation and the difficulty of application to widespread lesions. All patients with physical signs suggesting infection were treated, so the possibility that some lesions might have recovered spontaneously cannot be excluded.

There were 164 episodes of symptomatic bacterial infection affecting 40% of 190 children with atopic eczema during a two and a half year period. This does not include those treated by the general practitioner or those with uncertain response to treatment. The high hospital admission rate partly reflects the severity of some of these cases. It is also partly attributable to the local policy of using short admissions to initiate treatment and teach parents how to continue the same management at home. As in any hospital based study, the patients were selected and contained an excess of severe or intractable cases, but in this group infection was common and caused substantial morbidity.

The importance of *S aureus* as a skin pathogen is well known, but the frequency of concomitant infection with β haemolytic streptococci, 62% in this series, is less well appreciated. This high incidence of streptococci underlines the need for treatment of both streptococci and staphylococci in infected eczema. Flucloxacillin has antistreptococcal activity, and ought to be adequate as a single agent to deal with both bacteria. Previous local experience of treatment failure with flucloxacillin alone, however, led to the addition of phenoxymethylpenicillin. Erythromycin was avoided except in cases of penicillin allergy, because of the high incidence (18%) of erythromycin resistant staphylococci. Cefadroxil was sometimes used, as a single agent to cover both pathogens and having the advantage of requiring only twice daily dosage. The role of topical antiseptics, topical antiseptic-corticosteroid preparations, antiseptics in the bath, and intranasal neomycin and chlorhexidine cream are not clarified by this study.

Thirty two per cent of the β haemolytic streptococci were not Lancefield group A. The data do not distinguish between the relative pathogenicity of different strains of streptococci in atopic eczema, nor do they prove the individual importance of either streptococci or staphylococci. Treatment was directed against both organisms. Obtaining bacteriology swabs from the skin was atraumatic, but taking nose and throat swabs was disliked. The results indicate that taking nose and throat swabs is unnecessary, for it did not detect organisms that could not be more simply recovered from the skin, and did not influence treatment.

This study shows that it is common for bacterial infection to cause exacerbations of atopic eczema. The signs of infection are not always clear, and there is a case[7] for a trial of oral antibiotic treatment in any child with troublesome atopic eczema.

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C reactive protein in the evaluation of febrile illness

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SUMMARY We studied prospectively 154 febrile children to determine the diagnostic value of the quantitative serum C reactive protein concentrations (CRP). Children with acute otitis media, acute tonsillitis, or treated with antibiotics during the two previous weeks and infants less than 2 months of age were excluded. Ninety seven children were from private paediatric practice and 57 were patients who had been admitted to hospital. The comparison group consisted of 75 children with confirmed bacterial infections whose CRP values were recorded retrospectively. In the study group 35 (23%) children had a confirmed viral infection, 92 (59%) had a probable viral infection as judged from the clinical picture and outcome of the illness, and 27 (18%) had a bacterial or probable bacterial infection. When the duration of the disease was more than 12 hours and the CRP value less than 20 mg/l, all children had a confirmed or probable viral infection. Nine children (one from the study group and eight from the comparison group) were found to have a septic infection and a CRP value of 20 mg/l or less. In all these cases, however, the duration of the symptoms was less than 12 hours. In addition CRP ≤20 mg/l was found in five (14%) children with urinary tract infection in the comparison group. CRP values of 20–40 mg/l were recorded in children with both viral and bacterial infections. A CRP value ≥40 mg/l detected 79% of bacterial infections with 90% specificity. Our data show that determination of serum CRP concentrations is a valuable tool in evaluating children who have been ill for more than 12 hours.

Febrile children comprise one of the most important problems in paediatric practice. The major diagnostic goal is to distinguish bacterial and treatable infections from viral ones. Recent studies have shown serum C reactive protein (CRP) determination to be useful in the diagnosis of invasive bacterial infections.[1–3] We studied the value of CRP in evaluating febrile children with a special attention to respiratory virus infections.

Patients and methods

Study group. From March 18 to May 31 1984, 154 consecutive febrile children with respiratory tract infection or without localising signs of infection were studied prospectively. Of these, 97 were outpatients from private paediatric practice and 57 were patients who had been admitted to our Department of Pediatrics. Fever were defined as an axillary temperature of 38°C (100·4°F) or higher. Children with acute otitis media, acute tonsillitis, or treated with antibiotics during the two previous weeks and infants less than 2 months of age were excluded. Children with acute otitis media were excluded because they are routinely treated with antibiotics. Children with tonsillitis were excluded because a separate study was being carried out of tonsillitis.

There were 70 girls and 84 boys. Seventy eight (51%) children were less than 2 years old, 42 (27%) between 2 and 6 years, and 34 (22%) over 6 years old. The mean age was 3 years 4 months with a range of 2 months to 14 years.

The outpatients received a questionnaire for follow up of the symptoms and signs of the disease. Re-examination was performed in 83 of 97 outpatients seven days after the first visit, and the questionnaire was returned. The follow up was conducted by telephone in another 13 patients, and one patient returned the questionnaire by mail. The inpatients were treated in the hospital until afebrile and were not routinely re-evaluated.

Blood was taken for routine haematologic tests (total white blood cell counts (WBC) and differential counts, erythrocyte sedimentation rate (ESR), and CRP). Nasopharyngeal mucus aspirates for rapid diagnosis of virus was taken from 135 children.

Further studies were performed only on specific clinical indications. Urine analysis with culture was performed in 68 patients, throat culture for β haemolytic streptococci in 34 patients, blood culture in 29 patients, chest roentgenogram in 27 patients, bacterial antigen (*Haemophilus influenzae* type B, *Streptococcus pneumoniae*, *Neisseria meningitidis*) detection from the urine in 14 patients, lumbar puncture in 11 patients, and bacterial antigen detection in serum in eight patients. Pneumococcal antibodies from paired sera were studied in 20 children.

Comparison group. The comparison group for CRP concentrations, total WBC counts, and ESRs in bacterial infections included 75 children with proved bacterial disease treated in the same hospital from January 1 1982 to February 28 1984. The case records of these children were reviewed retrospectively. There were 22 boys and 53 girls, and the mean age was 2 years 9 months with a range of 2 months to 16 years. Thirty six patients had urinary tract infection (bladder tap culture positive), 21 meningitis (spinal fluid culture positive), 11 epiglottitis (blood culture positive), five septicaemia, and two cellulitis with a positive blood culture.

Determination of CRP. The CRP values of the patients who had been admitted to hospital were determined on admission quantitatively by turbidometry (Multistat III, IL) using standards from Behringwerke AG and antiserum from Dakopatts AS. In the outpatients the CRP was quantified with a rapid liquid phase immunoprecipitation technique[4] using reagents (CRP kit cat no D-147 and CRP Buffer cat no D-179) from Orion Diagnostica, Finland.

Enzyme immunoassay for viral antigens. Nasopharyngeal secretion specimens were collected by suction through nostrils with a disposable mucus extractor (Vygon, Ecouen, France). The specimen volume obtained was usually 0·5–2·0 ml. The specimens were tested parallel for respiratory syncytial virus, adenovirus, influenza A and B virus, and parainfluenza virus type 1, 2, and 3 antigens by analogous enzyme immunoassays. The indirect enzyme immunoassay was used as described previously.[5]

Enzyme immunoassay for pneumococcal antibodies. IgM, IgA, and IgG antibodies to pneumococci were assessed by an enzyme immunoassay with a 14 valent pneumococcal polysaccharide vaccine (Pneumovax^R; Merck, Sharp and Dohme) as antigen. The antigen was coupled (1·4 μg/ml) onto polystyrene microtitre plates (Linbro/Titertek, Flow Laboratories, Hamden, Connecticut). The coupling buffer was 0·05M phosphate buffered saline (pH 7·4). The same buffer supplemented with 1% normal sheep serum was used for saturating the plates and as an assay buffer. Sera were diluted 1:100 for incubation. After incubation conjugated antibodies to human IgM, IgA, or IgG (Orion Diagnostica, Espoo, Finland) were added. P-nitrophenylphosphate (Orion Diagnostica) was used as substrate, and the optical density was measured at 405 nm by a vertical beam photometer (Titertek/Multiskan, Eflab Oy, Helsinki, Finland). A standard curve was prepared for each immunoglobulin class. The results were expressed as relative units (EIU), where one unit was 1/100 of corresponding antibody concentration in the reference serum.

Statistics. Statistical analysis was carried out by the one way analysis of variance and the Tukey-Kramer method using logarithmic CRP and ESR values. P values less than 0·05 were considered significant.

Results

Disease range. In the study group 35 children (23%) had a confirmed viral disease, 27 (18%) had a bacterial or probable bacterial disease, and 92 (59%) had a probable viral infection. Sixty (65%) patients with probable viral infection had respiratory symptoms. Eighty one (88%) of the children with probable viral infection recovered within a week without treatment with antibiotics. The remaining 11 patients were treated with antibiotics for various reasons.

The viruses found by direct antigen detection were parainfluenza type 3 (14 cases), influenza B (12), parainfluenza type 1 (7), adenovirus (3), and respiratory syncytial virus (1). One patient had both parainfluenza type 3 and respiratory syncytial virus simultaneously. One child had parainfluenza type 3 virus at the first visit and influenza B virus at the follow up visit. Table 1 shows the diagnoses of the patients. The aetiologic agent of all urinary tract infections was *Escherichia coli*. The causative agent in the two cases of meningitis was *Haemophilus influenza* type B, cultured from the spinal fluid and the blood. Sixteen children had lobar pneumonia with high fever, and they all responded to treatment with antibiotics within 12–24 hours, fulfilling the clinical criteria of bacterial pneumonia. Pneumococcal antibodies were raised in four of these patients (IgM 7·4–13·1, IgM 7·5–30·1, IgM 12·5–24·5, and IgA 0·6–22.3, respectively). One patient was positive for pneumococcal antigen in the urine and

Table 1 *Diagnoses of patients of the study group*

Outpatients (n=97)		*Patients who had been admitted to hospital (n=57)*	
Disease	*No*	*Disease*	*No*
		Proved or suspected viral diseases	
Upper respiratory tract infection	52 (19)*	Fever without localising signs	8 (1)*
Fever without localising signs	32 (6)*	Laryngitis	7 (4)*
Pharyngitis	3	Wheezy bronchitis	7
Urticaria	2	Upper respiratory tract infection	7 (4)*
Laryngitis	1	Febrile convulsions	3 (1)*
Wheezy bronchitis	1	Exanthem subitum	2
Exanthem subitum	1	Purpura non ultra descriptus	1
		Proved or suspected bacterial diseases	
Lobar pneumonia	2 (2)**	Lobar pneumonia	14 (4)**
Streptococcal pharyngitis	2 (2)**	Urinary tract infection	5 (5)**
Urinary tract infection	1 (1)**	Meningitis	2 (2)**
		Pneumococcaemia	1 (1)**

*Confirmed viral infection (positive for nasopharyngeal secretion).

**Bacterial culture or antigen detection in serum/urine positive or serologically confirmed bacterial infection.

Table 2 *C reactive protein values (CRP), white blood cell count (WBC), and erythrocyte sedimentation rate (ESR) in patients with bacterial, viral, and probable viral infections*

	CRP (mg/l)		*WBC count ($\times 10^9$/l)*		*ESR (mm/h)*	
	n	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*
Study group:						
Bacterial infections	27	98 (67)	27	18·1 (6·7)	23	57 (30)
Viral infections	35	13 (12)	35	8·5 (4·5)	32	16 (11)
Probable viral infections	92	17 (20)	92	9·2 (5·3)	84	16 (12)
Comparison group:						
Septic infections	39	115 (71)	39	18·7 (7·8)	31	46 (32)
Urinary tract infections	36	89 (61)	36	19·8 (6·3)	33	53 (33)

serum, and one patient had a positive blood culture for *Haemophilus influenzae* type B.

CRP, WBC count, and ESR. Table 2 shows the mean (SD) values of CRP, WBC count, and ESR. The differences between bacterial and viral diseases and probable viral infections were significant ($p<0·05$) in all these laboratory tests. There was no significant difference between viral and probable viral diseases, nor in bacterial infections between the study group and the comparison group.

Because CRP values may not begin to rise in some patients until 12–22 hours after onset of stimulus,[6] patients who had been sick for less than 12 hours were excluded from the calculations of the sensitivity and specificity of CRP, WBC count, and ESR for bacterial infections. In three patients of the study group the duration of symptoms was less than 12 hours; one had pneumococcaemia, one bacterial pneumonia (confirmed serologically), and one meningitis. One of these patients had CRP <20 mg/l. Table 3 shows the sensitivity, specificity, and predictive values of CRP, WBC count, and ESR for bacterial infections in the study group. Of the patients with viral or probable viral infection, 75% had CRP less than 20 mg/l. Of the patients with CRP $\geq$40 mg/l, 59% had bacterial infection, and 90% of patients with viral or probable viral infection had CRP <40 mg/l (Figure).

Of the patients with bacterial disease, 67% had WBC count $\geq 15\times 10^9$/l, and 87% of patients with viral or probable viral infection had WBC count $<15\times 10^9$/l. ESR $\geq$30 mm/h detected 91% of patients with bacterial infections, and 89% of patients with viral or probable viral infection had ESR <30 mm/h.

In the comparison group there were eight patients with septic bacterial infections with duration of symptoms for less than 12 hours and CRP $\leq$20 mg/l. In addition there were five children with urinary tract infection with CRP $\leq$20 mg/l.

Outcome and treatment. Eighty three outpatients attended the follow up visit. Eight children had otitis

Table 3 *Sensitivity,* specificity,† positive predictive value,‡ and negative predictive value§ of C reactive protein concentrations (CRP), white blood cell count (WBC), and erythrocyte sedimentation rate (ESR) for bacterial infections in the study group of 151 children who had been ill for more than 12 hours (values are %)*

		Sensitivity	*Specificity*	*Positive predictive value*	*Negative predictive value*
CRP* (mg/l)	≥20	100	75	43	100
	≥40	79	90	59	96
	≥80	63	98	88	93
WBC (×10⁹/l)	≥10	96	66	35	99
	≥15	67	87	50	93
	≥20	38	97	69	93
ESR (mm/h)	≥30	91	89	61	98
CRP* (mg)l/WBC (×10⁹/l):					
	≥20/≥15	67	95	70	94
	≥40/≥15	58	96	74	92
	≥80/≥20	33	100	100	89
ESR (mm/h)/WBC (×10⁹/l):					
	≥30/≥15	59	95	68	92

*Probability that test results will be positive when bacterial disease is present.
†Probability that test results will be negative when bacterial disease is not present.
‡Probability that bacterial disease is present when results of test are positive.
§Probability that bacterial disease is not present when results of test are negative.[20]

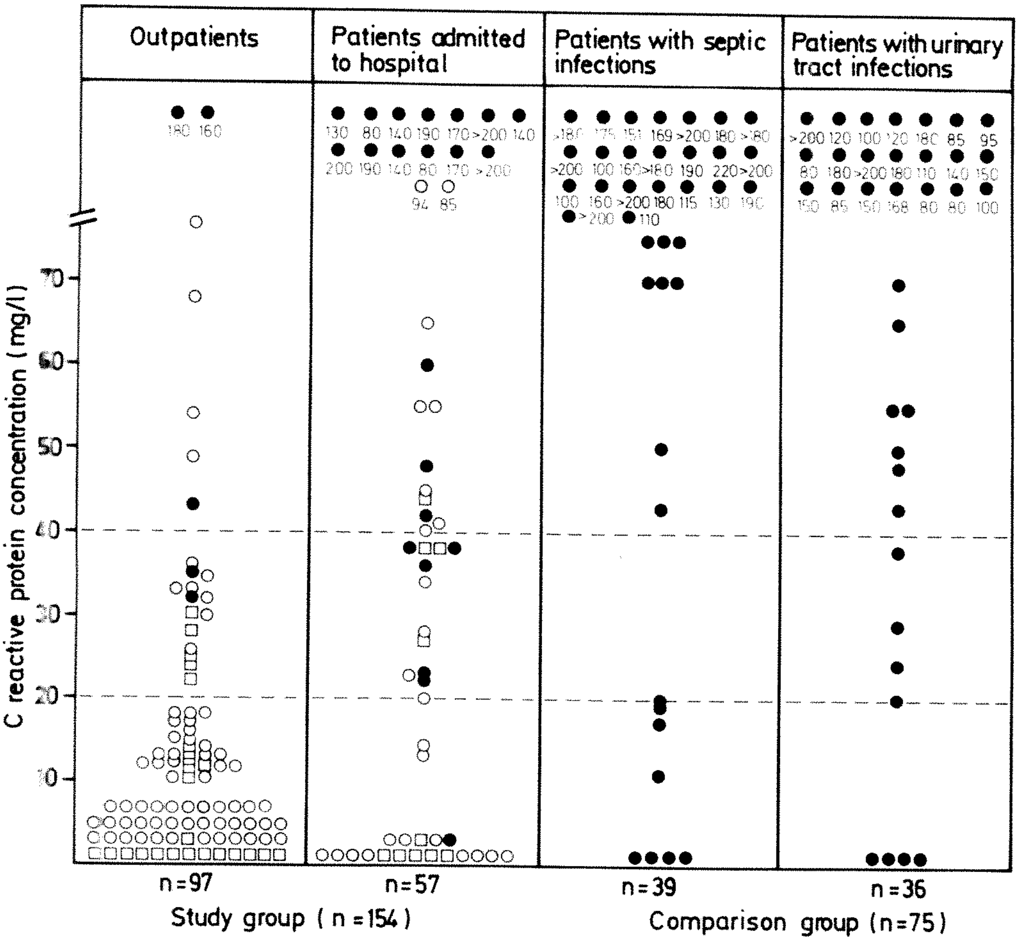

Figure *Serum C reactive protein concentrations of patients in the study and the comparison groups (●=bacterial infection, □=confirmed viral infection, ○=probable viral infection).*

media, six of whom had had a confirmed viral disease at the first visit. Fourteen children had minor respiratory symptoms, and one had wheezy bronchitis. All but one of the children with a new viral infection (influenza B) and otitis were afebrile. The children contacted by phone or by mail had recovered uneventfully.

Seven of the 97 outpatients were treated with antibiotics at the first visit. Of these, two had alveolar pneumonia, one had urinary tract infection, and two had influenza B virus infection. Two patients with streptococcal pharyngitis were treated after their throat culture proved positive. In the other eleven outpatients treated, antibiotics were started during follow up or at the follow up visit. Eight of the treated children had acute otitis media, one had lymphadenitis, one had upper respiratory tract infection, and one had a positive throat culture for β haemolytic streptococci group G, although she did not have pharyngitis. All 22 bacterial infections of patients who had been admitted to hospital were treated with antibiotics. Altogether, 18 outpatients (19%) and 32 patients who had been admitted to hospital (56%) were treated with antibiotics.

Discussion

This study differs from previous studies of CRP in that rapid detection of respiratory virus antigens in nasopharyngeal mucus permitted us to diagnose the specific viral aetiology within 30 hours in 35 (23%) patients. The results show that the quantitative CRP test is a valuable tool for distinguishing viral infections from bacterial infections in febrile children. If the duration of the illness was more than 12 hours and the CRP value was less than 20 mg/l all children investigated had viral or probable viral infection. Seventy six (78%) of the 97 febrile children studied in private practice and 19 (34%) of the patients who had been admitted to hospital belonged to this group. There were nine children (one in the study group and eight in the comparison group) with CRP ≤20 mg/l who had an invasive bacterial infection. In all cases the duration of the disease was 12 hours or less, which suggests that the CRP test is good for screening only in patients who have been sick for more than 12 hours. McCabe and Remington reported CRP values less than 20 mg/l in 14% of 36 patients with bacteraemia.[7] The study, however, did not report the exact duration of the symptoms of the patients. CRP was ≤20 mg/l in five (14%) of the patients with urinary tract infection in the comparison group of this study, suggesting that the infection would have been in bladder level. Jodal *et al* have shown that serum CRP concentrations will not increase in cystitis.[8]

A CRP value exceeding 20 mg/l has been suggested as a screening limit for bacterial infections.[1] In this study we found its sensitivity for bacterial infection to be 100%, but the false positive rate was 25% and the positive predictive value only 43%. Our data prefer CRP value 40 mg/l as a screening limit, because its specificity (90%) and positive predictive value (59%) are better and sensitivity is still 79%. Raised CRP values (≥40 mg/l) were found in one (3%) of 35 patients with confirmed viral infection and in 13 (14%) of the 91 patients with probable viral illness. We have shown previously that in children who were admitted to hospital with adenovirus, influenza, parainfluenza, or respiratory syncytial virus infection CRP values more than 40 mg/l were recorded in 38%, 20%, 0%, and 13% of patients, respectively.[9] Some of these patients may have undergone a concomitant bacterial infection, which remained undiagnosed. On the other hand, it is probable that some viral infections, especially adenovirus infections,[10] may induce so much tissue damage that CRP values will be raised.

Many previous studies have evaluated the value of WBC count, ESR, and CRP in the detection of serious bacterial infections.[11-15] No test alone or in combination has 100% sensitivity and specificity for bacterial infections. Rasmussen and Rasmussen have shown that WBC and differential counts have little value in distinguishing bacterial infections from viral infections.[11] McCarthy *et al* found a clinically useful association between a WBC count $\geq 15 \times 10^9$/l and ESR ≥30 mm/h and pneumonia or bacteraemia in children less than 2 years old with temperatures ≥40°C.[16] In a further study they showed that ESR ≥30 mm/h was more sensitive than a positive slide test for CRP (1:50) in bacteraemia, pneumonia, and other bacterial infections, but it was less specific than a positive CRP test or a high WBC count.[17]

In this study the best single indicator of bacterial infection was ESR ≥30 mm/h with a sensitivity of 91% and a specificity of 89% (Table 3). In confirmed viral and probable viral infections ESR was less than 30 mm/h in 89% and 88%, respectively. The differences between ESR ≥30 mm/h and CRP ≥40 mg/l, however, were small, and the CRP test has several other advantages over ESR. CRP can be measured quantitatively with a simple and inexpensive method in 15 minutes.[4] It increases within hours and, most important, CRP decreases during successful treatment with a half life of three days.[18] The decrease is much more rapid than that of ESR.[12] The rapid decrease of CRP permits the use of this test during the follow up of patients with bacterial infections. Peltola *et al* have recently shown that a reincrease of CRP during the treatment of bacterial meningitis reflects complications.[19]

The determination of CRP combined with a careful clinical examination was useful when the necessity of treatment with antibiotics was being considered. Only seven of 97 outpatients were treated with antibiotics at the first visit. The uneventful recovery of 79 (88%) of the untreated outpatients justifies our antibiotic policy.

In conclusion, our data show that determination of CRP is a valuable tool in evaluating febrile children. When the duration of the illness is 12 hours or more and serum CRP concentration less than 20 mg/l and there is no identifiable focus of bacterial infection—that is, otitis, tonsillitis, cystitis, etc—the disease is most probably a benign viral infection. CRP values of 20–40 mg/l may be recorded both in viral and bacterial infections. Most febrile children with CRP $\geq$40 mg/l have a bacterial infection. Finally, it should be emphasised that no laboratory test will replace careful clinical judgment of a febrile child.

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Comparison of desmopressin and enuresis alarm for nocturnal enuresis

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SUMMARY Fifty children with primary nocturnal enuresis were randomised for a study comparing desmopressin (DDAVP) and enuresis alarm. Forty six completed the trial, 24 of whom were treated with 20 µg intranasal desmopressin nightly and 22 with enuresis alarm for three months. Failures were crossed over and relapses were continued on the same treatment for a further three months. The improvement rate was 70% in the group given desmopressin and 86% in the group treated with alarm; the difference was not significant. During the first week of treatment the group given desmopressin was significantly dryer, and at the end of the study 10 of these patients relapsed compared with one patient in the group given the alarm. No serious side effects were observed.

This study confirms the role of conditioning treatment as preferable in long term treatment of nocturnal enuresis. When this fails or when a safe drug with rapid effect is needed, however, desmopressin is a useful alternative.

Bedwetting among children is a common disorder, affecting 30% at age 4, 10% at age 6, 3% at age 12, and 1% at age 20.[1] Untreated, the spontaneous cure rate is about 15% a year.[2] Treatment is dominated by two approaches, enuresis alarm and drugs.

The enuresis alarm was invented by Pfaundler in 1904.[3] Since then many studies have shown the benefit of these devices,[3–5] and a recent study comparing different mechanisms showed no important difference in their efficacy.[6] Treatment usually results in an initial cure in 65–100% of cases with a relapse rate of 9–47%. Modern devices are free of the adverse effects of earlier models such as erythema and 'buzzer ulcers'.[7]

Treatment with drugs has largely been focused on tricyclic antidepressants especially imipramine or, more recently, antidiuretic agents such as desmopressin (DDAVP). For imipramine the proportion of total remission is 10–50% during treatment and a long term cure in 5–40%.[8] However, numerous reports of side effects, some lethal, have led to a decline in its use.[9]

Since Dimson in 1977 reported on the effects of desmopressin[10] several double blind, placebo controlled studies have shown the efficacy of the drug often with rapid effect but also often with immediate relapse after ending treatment.[11–16] The drug seems to be safe with few side effects. As this drug has not been compared with other treatments for nocturnal enuresis and as no long term studies have been done this study compared the efficacy and safety of desmopressin with an enuresis alarm in a controlled, randomised study of three months' duration.

Materials and methods

Between January 1982 and August 1983, 87 children with nocturnal enuresis were referred to my office and were screened for entry into the study. Inclusion criteria were: boy or girl older than 6 years; not dry for more than six months after the third year; at least three wet nights a week during observation period; and written, informed parental consent. Exclusion criteria were: treatment for enuresis during previous year; day enuresis; cardiovascular disease; renal disorder; neurological disease; and chronic urinary tract infection.

Of the 56 patients who qualified for randomisation, six chose not to participate. After written and oral information, parental consent was obtained from the remaining 50 patients who were randomised to three months' treatment with either an enuresis alarm (Eastleigh A1 or A1P with wire mesh pad, N H Eastwood and Son Ltd, London, or Sesam Dry-Bed with aluminium tape plastic pad, Astric Products Ltd, Brighton) or a bedtime dose of 20 µg desmopressin (Minirin intranasal solution, Ferring Pharmaceuticals, Mälmo, Sweden) given by calibrated nasal catheter (Rhinyle). All patients completed a questionnaire. A complete history was taken and physical examination performed. Before and on ending the 3 months' treatment the following laboratory tests were performed: white blood count, sedimentation rate, and serum electrolytes, haemoglobin, and creatinine concentrations. On the same occasions and after four weeks' treatment, a urine sample was taken for culture, density, and osmolality in urine voided at 0500. All patients kept a diary card to note nocturnal events during treatment, including a two week observation period before and at the end of the study. About four weeks after treatment all patients were followed up and all relapses recorded. Patients were instructed to report relapses during the following two months, and these relapses were included in the final result. Patients who did not respond to given treatment were crossed over to the opposite treatment for another three months. Patients who relapsed during the three months after treatment were given the same treatment for a further three months.

Statistical methods. Wilcoxon rank sum test was used to compare the results of individual patients before, during, and after treatment. The outcome of the two groups was compared using the χ^2 test. Student's t test was used to compare laboratory values in and between the groups and to compare the mean result of the two groups week for week during treatment.

The study protocol was approved by the Department of Drugs of the National Board of Health and Welfare and the ethical committee of Malmö-Lund University.

Results

Distribution of the social classes of the parents in the two groups was similar.

After the start of the study one girl in the group given desmopressin and one boy in the group given the enuresis alarm withdrew. In the group given the enuresis alarm one girl who developed urinary tract infection and one boy who became dry before he started treatment were excluded, leaving 24 patients in the group given desmopressin and 22 in the group given the alarm.

The enuresis score was calculated from score tables kept at home (dry=1, a little wet=2, very wet=3). Success was defined as less than five wet nights during the last 28 nights (average one wet night or less per week) or significantly lower enuresis score. In this way even patients who were much more dry than before but still a little wet were counted as clinically significant improvements and therefore as successes. During treatment there was no difference between treatment groups, but due to higher frequency of relapse in the group given desmopressin the result for the group given the alarm was significantly better both during the first two weeks after ($p<0{\cdot}02$) and three months after treatment ($p<0{\cdot}001$).

The number of dry nights was analysed week by week during the study. The Figure shows the results. During the first treatment week (week 3) patients treated with desmopressin showed immediate improvement and registered significantly more dry nights than patients in the group given the alarm ($p<0{\cdot}001$). This trend continued for three weeks. During the last nine weeks the group given the alarm was drier, but this difference was only significant ($p<0{\cdot}002$) in the 11th week. After treatment both groups were significantly dryer than before, but the group given the enuresis alarm was more so ($p<0{\cdot}001$ and $p<0{\cdot}02$ for the group given the alarm and the group given desmopressin against baseline, respectively). The results were not different when analysed according to age or sex.

One patient treated with enuresis alarm relapsed after treatment. New treatment with enuresis alarm

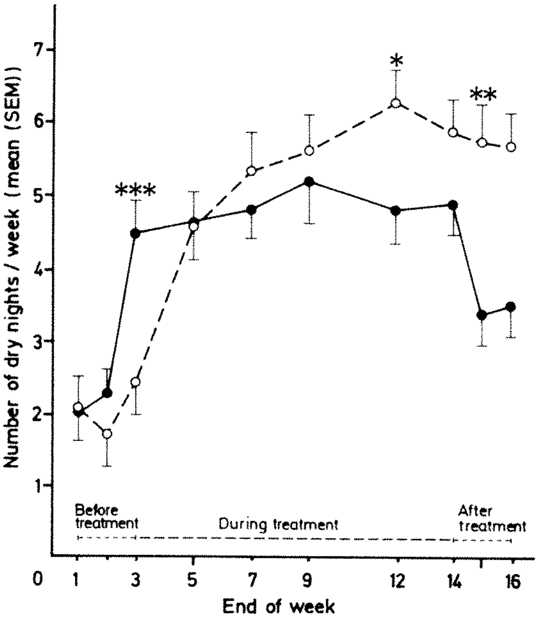

Figure *Number of dry nights per week before, during, and after treatment with either desmopressin (●—●; n=24) (*p<0·05; **p<0·01; ***p<0·001) or enuresis alarm (○—○; n=22).*

was without effect. Ten patients who relapsed after treatment with desmopressin were given treatment for a further three months, which proved successful in seven. Four of these patients relapsed immediately after treatment and another within the next two months, leaving two of the 10 patients with a better result after six months' treatment. The number of patients who improved on long term treatment was now 10 (42%) of the group given desmopressin and 18 (82%) of the group given the alarm.

Those who failed to respond to the first treatment regimen were crossed over to the opposite treatment. In the group crossed over from treatment with desmopressin five children did not respond to the alarm, two improved, and by the two month control three were better than before. Of three children who did not respond to the alarm, two improved on treatment with desmopressin, but both relapsed. There was no significant difference between treatment results during or after treatment. One child treated with the alarm dropped out after three weeks owing to no improvement.

There were no significant differences in the results of laboratory tests or blood pressure measurements between or within the groups, except for urine osmolality and density, which were significantly higher during treatment with desmopressin and urine osmolality in the group given the alarm, which was lower during treatment than before. Results of urine cultures and chemical tests were negative in all patients.

No serious adverse effects were registered in any group. In patients treated with desmopressin for three months five (13%) complained of nasal discomfort and one (3%) had occasional nose bleeds. Two patients (5%) experienced a bad taste in the throat. Side effects in the group given the alarm were minor but more frequent; 21 patients (78%) complained of false alarms and five (19%) that the alarm did not work when the child wet the bed. In addition 15 (56%) stated that the alarm did not awake the child and 15 (56%) that other members of the family woke instead. One child was frightened of the alarm.

Discussion

There are only a few controlled studies comparing enuresis alarms with medical treatments. One recent study found alarms to be superior to treatment with imipramine.[17] In this study the success and relapse rates were similar to those of earlier studies of treatment with both alarms and imipramine.[9]

In the present study desmopressin gave better results during the first three weeks, showing that it has an immediate effect. As in earlier studies most patients relapsed after treatment, but in this study the frequency of wet nights was still significantly lower after treatment compared with before for both groups, although significantly more so for the group given the alarm. In both groups the success rate was superior to the spontaneous cure rate (15% per year), which would have cured less than two patients in each group during the study period.

There has been discussion about how desmopressin works. Birkasova *et al* postulated that the effect was due to the antidiuretic effect of the drug.[14] Aladjem *et al*, however, did not find any rise in morning urine osmolality during treatment;[12] but these measurements were made on urine samples from late morning after the bladder had been emptied of the previous night's urine. In my study parents took urine samples from their children at 0500. In these samples, a significant increase of osmolality of morning urine was found during treatment with desmopressin. These findings support the hypothesis that the effect of desmopressin results from its antidiuretic effect. Surprisingly, in the group given the alarm urine osmolality decreased during the study, a result which may indicate that as the patients became drier their confidence grew so that they relaxed the restriction on their evening liquid intake.

As in other studies using desmopressin the drug did not have any clinically significant adverse effects. In contrast, the reports on adverse effects from treatment with imipramine are common. In a recent review article tricyclic antidepressants were reported to be the commonest cause of fatal poisoning in children.[9] Older children have died from overdose of imipramine both accidentally and in the belief that a greater dosage gives a better effect. All of this suggests that treatment with tricyclic antidepressants does more harm than good and has no place in the management of childhood enuresis. There is no doubt, however, that treatment with desmopressin offers many benefits. It is safe, has a rapid onset of action, and in about 30% of cases produces lasting improvement after treatment is stopped. I believe that the enuresis alarm is the first choice for treatment, but when this fails or is impracticable and a safe, practical alternative is needed desmopressin is useful.

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Evaluation of a developmental screening system for use by child health nurses

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SUMMARY An adapted version of the Woodside system for screening general development of the child is being used by child health nurses as part of their routine duties. In the present paper the system is validated in terms of standardisation, reliability, and validity. The system was standardised on 444 children aged 0–4, the assessments being carried out by a fully trained child health nurse. The inter-tester reliability of the system was found to be at least 95%. The validation sample consisted of all 27 'abnormal' children, all 20 'doubtful' children, and 77 'normal' children, and a highly significant correlation was obtained between the Woodside subsection scores and the relevant Griffiths' scales subsection scores. The findings support initial impressions that the adapted Woodside system is accurate. It is recommended for use by child health nurses as part of their developmental surveillance.

The basic premise underlying paediatric developmental screening is that the earlier a dysfunction or defect is identified, the better will be the final outcome for mother or child, or both.[1-5] Early diagnosis is certainly important with hearing and visual dysfunction, as a delay in beginning appropriate intervention beyond the known 'critical' or 'sensitive' periods may result in irreversible damage or distortion.[6-8] The benefits in screening for general development are not so obvious, as similar critical periods do not seem to exist. Even so, early intervention will, in many cases, alleviate or improve a developmental dysfunction, while failure to intervene may compound the underlying problem.[9]

If screening for general development can be justified consideration should be given to the suitability of available screening instruments and to the personnel who will apply them. Until recently, developmental screening in Australia was left to the family doctor, who used his experience to make an unstructured assessment of a child. Today, the art and science of developmental screening has become more sophisticated, and its implementation has, in some places, been transferred from qualified medical practitioners to suitably trained, though lesser qualified, personnel. To improve reliability, screening instruments of a more formal nature and with predetermined referral criteria have been devised. One such screening instrument is the Woodside system,[10] which was devised ten years ago in Woodside, a suburb of Glasgow, Scotland. A version of the Woodside system, adapted for Australian conditions, was introduced seven years ago at the Mothers and Babies' Health Association* for use by child health nurses who were already involved in preventive care of children aged 0–5. The adapted Woodside system was found to be short and easily administered and could readily be incorporated into the routine duties of the nurses.

It remained, however, for the system to be standardised and validated for Australian children of different ages. The present study (begun in May 1980) evaluates the adapted Woodside system as it is used by child health nurses.

The Woodside system

The Woodside system uses four charts to provide a visual summary of the developmental progress of a child. The charts, covering the areas of 'Social', 'Hearing and language', 'Vision and fine motor', and 'Gross motor' development, are shown in Figure 1(a)–(d). They have been adapted for Australian conditions, mainly in the gross motor area.

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*Now part of the Child, Adolescent and Family Health Services, South Australian Health Commission.

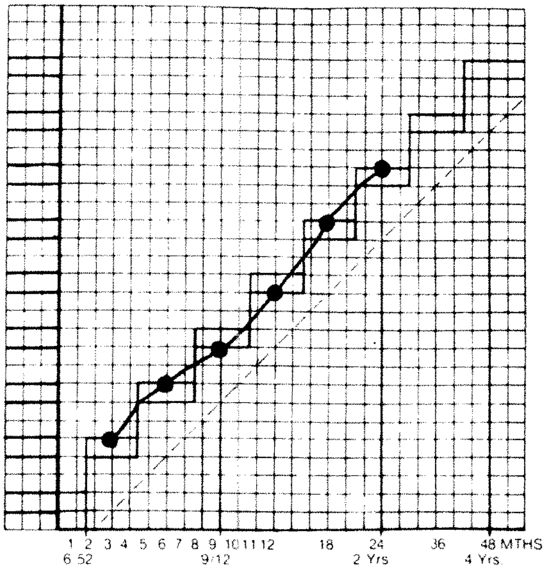
(a)

SOCIAL

1. Able to dress — except laces and back buttons (H).
2. Dry at night (H).
3. Washes hands (H).
4. Pulls pants up and down (H).
5. Drinks and replaces cup (H).
6. Knows parts of the body (4)
7. Drinks from cup without spilling (H).
8. Indicates toilet needs (H).
9. Puts cubes into box after being shown.
10. Finds toy under cup.
11. Rings bell.
12. Chews and swallows biscuit (observed). Copes with solid food.
13. Puts objects into mouth (cubes).
14. Reaches for and shakes rattle.
15. Responds to friendly face.
16. Enjoys being handled by mother (H).
17. Smiles when spoken to.
18. Some vocal sounds (H).

(H) — History of achievement sufficient.

Normal progress



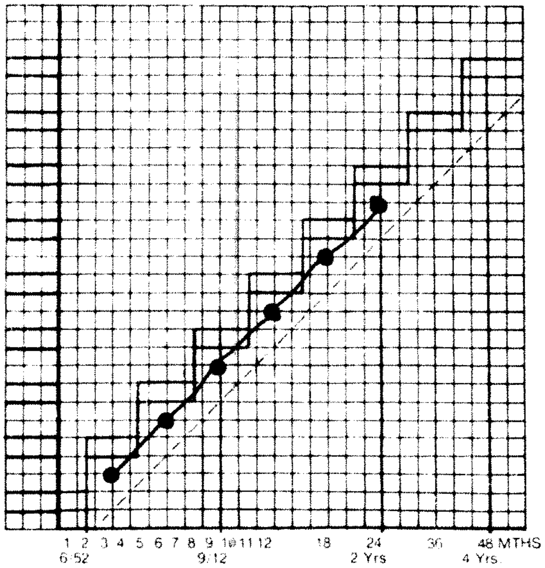
(b)

HEARING & LANGUAGE

1. 2 or more pronouns in conversation.
2. Grammatical speech articulated correctly.
3. Says first name.
4. Knows own sex.
5. Simple sentences (H).
6. Plays with miniature cup and saucer.
7. Points to parts of body.
8. Says five or more words (H).
9. Obeys simple commands, e.g. clap hands.
10. Says less than 5 words including "Mama" "Dada" "Baba" (if related to a person).
11. "Mamma" "Dadda" "Baba".
12. Hearing tests above ear level.
13. Unintelligible babble.
14. Hearing tests at ear level.
15. Turns eyes to sound.
16. Looks round meaningfully when spoken to.
17. Stills to bell.
18. Stills to mother's voice.

(H) — History of achievement sufficient.

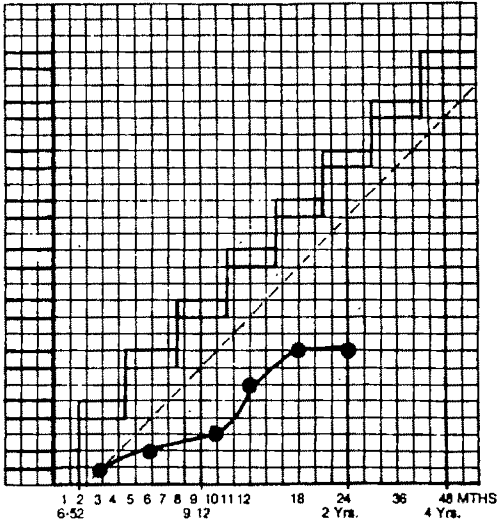
Doubtful progress



ⓒ

VISION & FINE MOTOR

1. Picks up and replaces very small objects, e.g. pins, with each eye covered separately.
2. Copies a square.
3. Copies a circle.
4. Builds a bridge of three bricks when shown.
5. Makes a vertical line when shown.
6. Makes a tower of six bricks when shown.
7. Makes a scribble on paper.
8. Makes a tower of three bricks when shown.
9. Pincer grasp using a small object e.g. Smartie.
10. Bangs bricks together when shown.
11. Side of finger grasp using a small object, e.g. Smartie.
12. Matches cubes.
13. Picks up cube from table or hand.
14. Transfers cube from one hand to another.
15. Holds a pencil briefly.
16. Follows a moving person with eyes.
17. Follows a moving face with eyes.



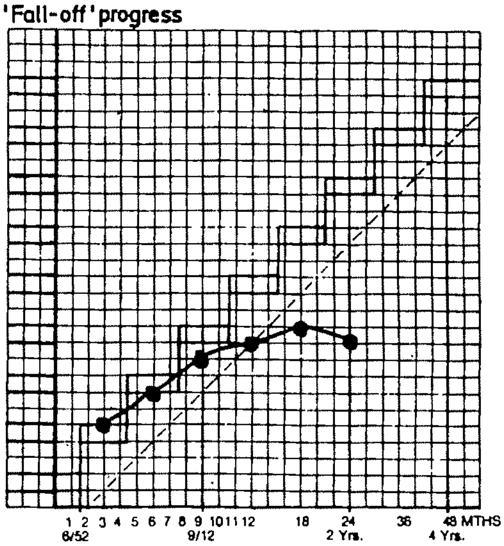
Abnormal progress

ⓓ

GROSS MOTOR

1. Stands on one leg 3-5 seconds.
2. Hops.
3. Stands on leg momentarily.
4. Walks on tiptoe (H).
5. Runs on whole of foot.
6. Kicks ball.
7. Picks object from floor without overbalancing.
8. Kneels without support (H).
9. Pulls to standing on furniture.
10. 'Cruises' round furniture.
11. Sits steadily on floor without support for few mins. (H)
12. Stands holding on to furniture.
13. Sits against wall or hand-no lateral support — 2/3 secs.
14. Hold round waist, lower abruptly exclude scissoring.
15. Pull from lying. Little or no head lag.
16. Ventral suspension. Holds head above plane of body.
17. Ventral suspension. Head in plane of body.

(H) — History of achievement sufficient.



'Fall-off' progress

Fig. 1 *Charts used in Woodside system to provide a visual summary of the developmental progress of a child: (a) Social; (b) Hearing and language; (c) Vision and fine motor; and (d) Gross motor.*

On the horizontal axis of each chart is shown the age of the child, with a range from 6 weeks to 4 years. The vertical axis contains a variety of tests set out in pairs with the pairs corresponding to appropriate ages and forming a step pattern across the chart. In each of the four charts a child's developmental ability is plotted against the age of the child. In practice there is a minimum total of eight test items to be applied for any individual child—that is, two test items for each of the four developmental areas.

With, for example, a 9 month old child being assessed using the chart on 'Social' development, a mark is made on the upper level of the step if the child succeeds in both test 11 and in test 12, and at the lower level of the step if he or she succeeds in only one of them (in Figure 2, these two marks are represented by O and o, respectively). If tests 11 and 12 are both failed, the child is assessed on tests 13 and 14, which are normally accomplished by a 6 month old child. Success at one or both of tests 13 and 14 is scored at the appropriate level (X or x in Figure 2). Tests 15 and 16 are applied if a child fails at tests 13 and 14 (scored V or v in Figure 2). For a bright child tests 9 and 10 might be attempted, which are normally accomplished by a 12 month old (scored Y or y in Figure 2). This last procedure is not recommended routinely as the object is to identify delay rather than bright children.

The assessments recorded on the individual charts are interpreted as follows: if the marks on the chart lie on or above the step the child's development in the particular area is suspected to be normal; if the marks lie between the step and the dotted, or 'threshold' line, development is considered to be doubtful; and if the marks lie on or below the dotted line, development is suspected to be abnormal/delayed.

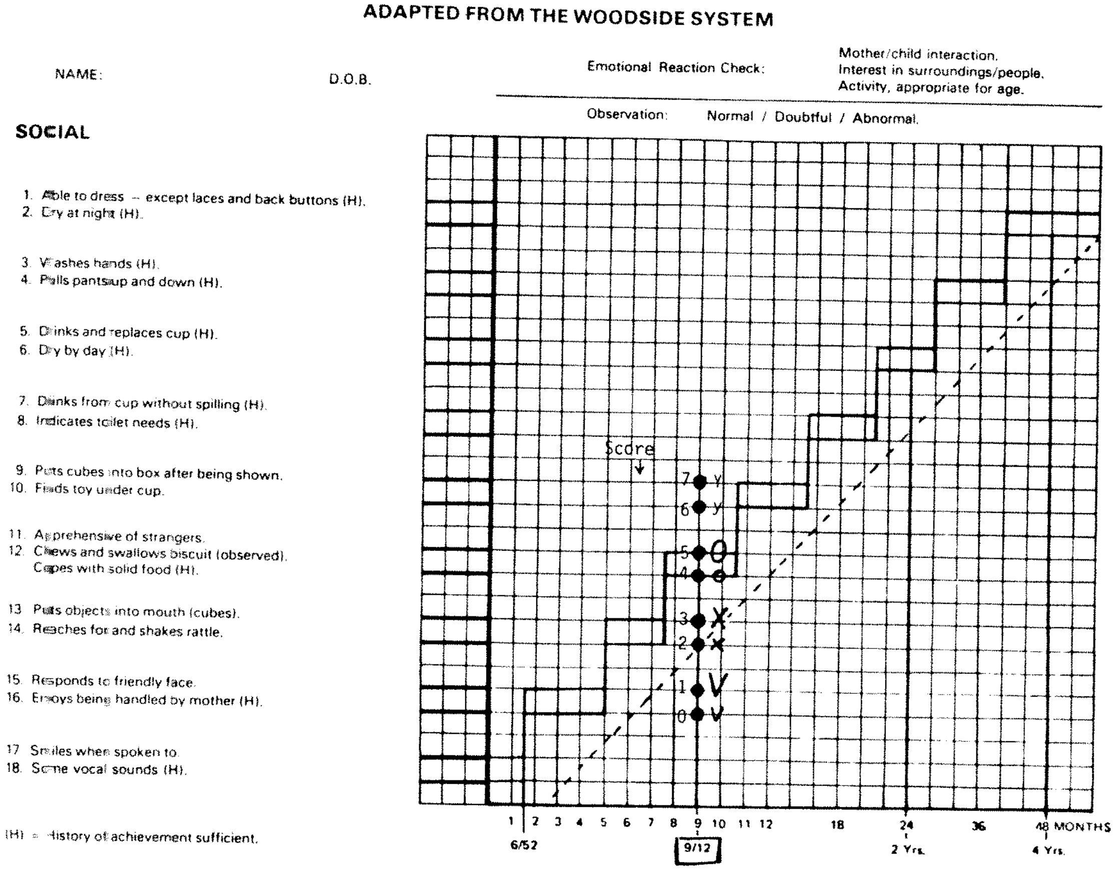


Fig. 2 *Example of a 9 month old child assessed for social development (see text for explanation).*

When the assessment plot lies on or below the dotted line in the first year of life the child's development is delayed by roughly three months; in the second year it is delayed by six months; and in the third and fourth years it is delayed by 12 months. For purposes of computer analysis in the present study, a score was allocated to the levels of attainment (in Figure 2)—that is, Y=7, y=6, O=5, o=4, X=3, x=2, V=1, and v=0.

Criteria which are used to decide whether a particular child should be further followed up or referred for appropriate diagnostic assessment are:

(1) If a total of two or more doubtful marks are recorded from the four areas of assessment the child is referred for a full diagnostic assessment.

(2) In the event of one doubtful mark being recorded in the area of 'Gross motor' development, the child is reassessed in two months' time.

(3) If one or more abnormal/delayed marks are recorded the child is referred for a full diagnostic assessment.

(4) If there is a 'fall off' in development from normal at one assessment to doubtful or abnormal/delayed at a subsequent assessment the child is also referred for a full diagnostic assessment.

The system is most helpful for regular, routine screening as it can be seen at a glance how a particular child is developing. Figure 1(a) shows normal progress, Figure 1(b) doubtful progress, Figure 1(c) abnormal/delayed progress, and Figure 1(d) a gradual fall off in progress.

Sources and methods

Subjects. The total number of children screened on the adapted Woodside system was 444, of whom 224 were boys and 220 were girls. Their ages ranged from 6 weeks to 4 years.

To obtain a normal distribution of children, the clinics from which they were drawn were situated in a range of high, medium, and low socioeconomic areas of the suburbs of Adelaide. Socioeconomic state of individual children was designated according to the employment, educational level, and housing condition of the parents of the children.[11] Altogether, 139 children (72 boys and 67 girls) were categorised as being of high socioeconomic state; 184 children (87 boys and 97 girls) as being of medium socioeconomic state; and 121 (65 boys and 56 girls) as being of low socioeconomic state.

Also studied were 17 confirmed abnormal children from a spastic centre, who were not included in the normal distribution group. There were nine boys and eight girls, and their age range was from 1 year 10 months to 4 years 4 months.

There were 52 children from ethnic groups, mainly Italian and Greek, which is a representative sample of the Adelaide metropolitan population. Of the 52 children (12% of the total of 444), 11 were of high socioeconomic state (8% of 139), 18 of medium socioeconomic state (10% of 184), and 23 of low socioeconomic state (19% of 121).

Methods

A child health nurse screened 461 children (the 444 children in the sample and the 17 known abnormals) using the adapted version of the Woodside system.* Training of the nurse in implementing the assessment was considered to be complete when there was a 95% agreement with BSLE in the scoring of 10 consecutive children. Details of the application of the Woodside system is described above.

In each of the four areas of development a child was given a score from 0–7 (as described above) on the adapted Woodside system. Scores of 2 or less in any one area or 3 in two or more areas were classified as 'suspected abnormal'; a score of 3 in one area was classified as 'suspected doubtful'; and a score of 4 or more in all areas was classified as 'suspected normal'.

The reliability of the adapted Woodside system was assessed, firstly, with two different testers assessing an individual child on separate occasions yet within a time interval of two weeks (50 children with an age range of 6 weeks to 4 years were assessed likewise), and, secondly, with the same tester assessing an individual child on two occasions one week apart (30 children).

A diagnostic assessment, using the Griffiths' scales criterion test,[12 13] was performed on all children deemed 'suspected doubtful' or 'suspected abnormal' by the Woodside screening assessment, and on at least 10% of the total number deemed 'suspected normal'. The diagnostic assessments were performed by two psychologists, a paediatrician, and BSLE, and all assessments were made within two weeks of the nurse's screening assessment with the Woodside system.

Vision and hearing were screened by a child health nurse using the Stycar method. The referral criteria for this screening has been previously described.[14] Height, weight, and head circumference were measured on all children, and a physical medical examination was performed on 426 children (96%).

Results

Table 1 shows the normative data for the four areas

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*Full details of the adapted Woodside system can be obtained from BSLE.

Table 1 *Woodside normative data in terms of means (SD) according to socioeconomic groups*

Socioeconomic group	*Social*	*Hearing and language*	*Vision and fine motor*	*Gross motor*
High (n=139)	4·6 (0·6)	4·6 (0·8)	4·7 (0·7)	4·7 (0·9)
Medium (n=184)	4·7 (0·8)	4·8 (0·9)	4·7 (0·9)	5·1 (1·0)
Low (n=121)	4·7 (1·1)	4·4 (1·1)	4·4 (1·1)	4·8 (1·1)

of the adapted Woodside ('Social', 'Hearing and language', 'Vision and fine motor', and 'Gross motor' development) obtained in Adelaide children of different socioeconomic groups.

The reliability of the adapted Woodside system calculated as the percentage agreement in the scores obtained on individual children by the same tester performing the test on two occasions one week apart, was 95·5%. The percentage agreement of two different testers making their assessments within two weeks of each other was 95·0%.

Table 2 *Correlation between Woodside (screening) system and corresponding Griffiths' (criterion) test in the four areas of development in 124 children*

Area of development	*Correlation 'r'*
Social	0·46*
Hearing and speech	0·69*
Vision and fine motor	0·65*
Gross motor	0·76*
Total	0·73**

*p<0·001. **p<0·05.

Table 3 *A 2×2 contingency table showing the number of abnormal scores on the Woodside system against the relevant corresponding Griffiths' score*

Woodside	*Griffiths*		*Total*
	Abnormal	*Normal*	
Abnormal	22	5	27
Normal	5	72	77
Total	27	77	104*

*Excluding 20 doubtful cases.
Co-positivity (sensitivity) 22/27=0·81. Co-negativity: (specificity): 72/77=0·94.
Over-referrals=5/124=4%, or 5/104=4·8% (excluding the doubtful cases).
Under-referrals=5/124=4%, or 5/104=4·8% (excluding the doubtful cases).

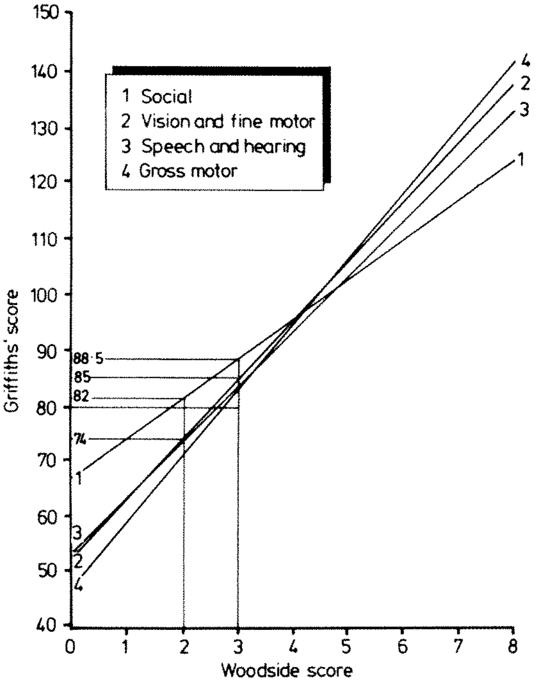

Fig. 3 *Regression lines for Woodside scores of social, vision and fine motor, speech and hearing, and gross motor developmental progress plotted against corresponding Griffiths' scores.*

Tables 2 and 3 and Figure 3 show the validation studies of the adapted Woodside system, expressed in terms of correlation coefficients, sensitivity (co-positivity) and specificity (co-negativity), over-referrals, under-referrals, and regression lines. A total of 124 children, comprising the 27 children assessed as 'suspected abnormal' on the Woodside system, the 20 assessed as 'suspected doubtful', and 77 assessed as 'suspected normal', were retested using the Griffiths' criterion test.

Figure 3 also shows the regression lines for the four areas of the Woodside system plotted against the Griffiths' scores. The four lines represent 'Social', 'Hearing and language', 'Vision and fine motor', and 'Gross motor' development. When considering any one of the four areas of development, a Woodside score of 2 had a corresponding Griffiths' scores (criterion test) of 74 or less in three of the four areas, except for the area of 'Social' development, where the relevant Griffiths' score was 82. It is reasonable, therefore, to suggest that a Woodside score of 2 would be an acceptable cut off point, as the corresponding Griffiths' score of 74 is just over 2 SD from the mean. Thus a Woodside score of 2 is categorised as 'abnormal'. (The Griffiths' test has a mean score of 100 and a SD of 12).

For a Woodside score of 3 the corresponding Griffiths' score was 85 or less in three of the four areas, except for the area of 'Social' development again, where the Griffiths' score was 88·5. A Woodside score of 3 corresponds with a Griffiths'

Table 4 *Classification of children identified from the Woodside screen according to socioeconomic group (n=444)*

Socioeconomic group	*'Normal'*	*'Doubtful and abnormal'*	*% age*
High	128	11	8·6
Medium	169	15	8·9
Low	100	21	21·0
Total	397	47	

score roughly 1 SD from the mean and is classified as 'doubtful'. A Woodside score of 4 relates to a Griffiths' score between 93 and 96, and a Woodside score of 5 relates to a Griffiths' score above 102. Of the 20 children assessed as 'doubtful' on the Woodside system, 15 were classified by the criterion test as 'abnormal' and five as 'normal'.

Of the 17 handicapped children included for comparative purposes, 13 had a Woodside total score (the combined scores of the four areas of the Woodside) of 0, with corresponding Griffiths' mean general quotient score of less than 50. The other four children had total scores of 11, 7, 3, and 2, with the corresponding Griffiths general quotient scores being 71, 78, 63, and 50, respectively. The mean score for the 17 children on the Griffiths' general quotient was 42 (SD=20).

In Table 4 the numbers of children classified as 'normal', 'doubtful', and 'abnormal' by the Woodside screen are listed according to their socioeconomic state. In the low socioeconomic group 21 children were classified as 'abnormal' or 'doubtful' on the Woodside system. Statistically, this is nearly twice the number that would be expected by chance ($p<0{\cdot}025$, $\chi^2=8{\cdot}04$).

The physical examination and the assessments of 'Hearing and vision' resulted in the referral of 14 physical defects (3% of 426), 48 suspected hearing disabilities (11% of 444), and 40 suspected visual disabilities (9% of 444).

Discussion and conclusions

The Woodside system adapted for Australian conditions and used by a child health nurse was found to be a valid instrument with a Pearson's correlation coefficient of $r=0{\cdot}70$ ($p<0{\cdot}05$) when compared with the widely accepted Griffiths' diagnostic test.

The highest correlations were in the areas of 'Gross motor' development ($r=0{\cdot}8$, $p<0{\cdot}001$), and the lowest in the area of 'Social' development ($r=0{\cdot}5$, $p<0{\cdot}001$). The latter findings could possibly be a consequence of the different environments of Glasgow and Adelaide. In Glasgow there is more limited indoor and outdoor living and recreation space as well as a poor climate, and it is suggested that there may be a greater pressure on the child to acquire acceptable social habits—for example, 'dry by day'—early.

Although 75% of 'suspected doubtfuls' were finally deemed to be 'abnormal', a close follow up of these children might be more appropriate than immediate referral. In this way developmental problems would not be missed, and parental anxieties associated with unnecessary over-referrals would be avoided. The cut off points between normal and doubtful and doubtful and abnormal may need reappraisal in the light of the recent observations by Hanson *et al* that the mean general quotient of the Griffiths' scales has increased.[15] Nationwide representative figures from Hanson *et al* are awaited.

The percentage of referrals for hearing (11%), vision (9%), and physical (3%) disabilities or defects are consistent with referral trends in two other Adelaide studies.[14] [16] These two studies were carried out on 4 year old children, and it is interesting to note that the referral rates for the various defects are similar to those in the present study of children aged 0–4.

The only other developmental screening test that has been validated and encompasses the 0–4 age range is the Denver developmental screening test.[17] The impression is, however, that the Woodside system is less time consuming to apply (with eight test items compared with between 12–26 test items for the Denver screen), gives a better visual record of the progress of a child, and has a chart that is more suitable for use with the same child on more than one occasion.

Sheridan has defined a handicapped child as one 'who suffers from any continuing disability of body, intellect or personality which is likely to interfere with his normal growth and development or capacity to learn'.[1] It is suggested that the Woodside system in the hands of trained child health nurses is a valuable instrument in helping to identify the present state of a child who may have a developmental handicap.

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When does secretory otitis media affect language development?

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SUMMARY Secretory otitis media is a very common disorder in early childhood, but its effects on language development are still uncertain. We describe 10 children with secretory otitis media and illustrate the wide range of disability attributable to this. It is suggested that the impact of secretory otitis media on language development depends on at least five factors: age of onset, duration of the episode(s), severity of the hearing loss, intrinsic qualities in the child, and the linguistic environment. The implications of this hypothesis for clinical practice and research are discussed.

Secretory otitis media is characterised by an effusion of variable viscosity behind an intact eardrum.[1] It is extremely common, and probably at least one third of preschool children suffer one or more episodes.[2] Some children have a single transient attack; others have repeated episodes, each followed by complete recovery; and a minority have the disorder for months or even years without any remission.[3] By far the most important clinical feature is hearing loss, which may vary from negligible to 50 to 60 dB, with a mean of 28 dB.[1] Pain in the ear may also occur, often in association with episodes of acute infection or with Eustachian tube dysfunction.

There has been much concern over the possible effects of middle ear disease on learning in general and language development in particular. This relation has been examined in over 30 published reports, and in most, significant correlations have been shown.[4-6] The majority of these studies, however, contain serious flaws in design. Most are retrospective, and therefore the precise diagnosis is often uncertain in the children with a history of ear disease; conversely the absence of previous ear disease in the control group cannot be shown. For the same reason, the number and duration of attacks, the severity of the hearing loss, and the distinction between unilateral and bilateral disease are seldom documented. Lastly, matching of cases and controls for psychosocial variables is seldom adequate, yet accurate matching is essential since the prevalence and perhaps the management of secretory otitis media are related to race, size of household, and social status, and these variables also influence development. It must therefore be said that the case for a cause and effect relation between secretory otitis media and learning problems remains unproved.[7]

Despite shortcomings of published research, most clinicians with an interest in this field are convinced that secretory otitis media is indeed an important cause of developmental problems in young children. The purpose of this paper is to present some illustrative case histories; to derive from these a working hypothesis on the nature of the relation between secretory otitis media and developmental problems; and to discuss the type of research design needed to investigate this hypothesis.

Methods and case reports

The children described here were seen in two children's audiology clinics over a three year period. They represent a small proportion of the total case load and were selected because they exemplify particular clinical problems. All except cases 4 and 7 lived in the catchment area of our hospital. The age when the child was first assessed by us is stated in each case. In all patients the diagnosis of secretory otitis media was based on the history, hearing tests, otoscopy, and impedance measurements, and in all except cases 9 and 10 it was subsequently confirmed at surgery. The details are summarised in the Table.

Hearing was tested by the most appropriate combination of the standard methods; distraction techniques, McCormick toy test (sometimes equivalent pictures were substituted), 'go' game, freefield audiometry, and pure tone audiometry. Only pure tone audiometry gives a direct measure of hearing

Table *Details of the 10 children with secretory otitis media (SOM)*

Case no (sex)	*Age when assessed (mths)*	*Probable age at onset of SOM (mths)*	*Minimum duration of episode (mths)*	*Estimated hearing loss (+=<30 dB) ++=30–45 dB +++=>45 dB)*	*Intrinsic language or learning problems (0–+++)*	*Environmental deprivation (0–+++)*	*Immediate postoperative improvement (0–+++)*	*Language catch up at follow up >6 months (0–+++)*
1 (M)	12	5	7	+++	0	0	++	+++
2 (M)	18	9	4	+	0	0	+	+++
3 (F)	66	36	30	+++	0	0	++	+++
4 (M)	38	?	?	++	0	++	+	+++
5 (F)	56	36 (?)	14 (?)	+	++	0	+	+
6 (F)	39	?	?	++	+	+++	+	++
7 (M)	35	12	23	++	+++	+	++	+
8 (F)	72	60	12	+++	0	0	+	0
9 (M)	22	21 (?)	1	++	0	0	0	0
10 (F)	34	30	4	++	0	0	0	0

loss, and with all the other techniques it is necessary to estimate the likely hearing loss. Sound levels were monitored with a sound level meter, and are stated in decibels sound pressure level (dB SPL). Language scores were all based on the Reynell developmental language scale which has two subsections, one for expressive language and one for comprehension.

Case 1. This 12 month old white boy was thought by his parents to have had a variable hearing loss from approximately 5 months of age. The onset was associated with a respiratory infection. He was said to hear loud sounds such as shouting, noisy music, or a football rattle but did not respond to quiet sounds. The parents described him as an unusually quiet baby.

Distraction testing produced responses to high and low frequency sounds at around 70 dB SPL but the responses were hesitant and were only confident and accurately localised at 75 to 80 dB SPL upwards. The diagnosis of severe secretory otitis media was confirmed at surgery shortly afterwards.

A substantial improvement in hearing was noted by the parents beginning about one week after surgery and he began to vocalise more freely. When tested two weeks later, distraction tests produced responses to 35 to 40 dB SPL to high frequency sounds and at 45 dB to low frequency sounds, indicating a considerable improvement in hearing. At 18 months of age he had several words with age appropriate understanding and normal hearing responses at low and high frequencies, but at 20 months there was evidence of further secretory otitis media and hearing impairment.

Comment

A hearing loss of this severity is unusual in secretory otitis media. The postoperative improvement in both responsiveness and vocalisation suggests that the hearing loss had inhibited the development of normal listening behaviour and would have affected language acquisition had it not been treated.

Case 2. This white boy aged 18 months had repeated episodes of acute otitis media starting at age 9 months. At 13 months grommets were placed because of persistent effusion. He was seen for assessment at 18 months because he had no speech, little 'jargon', and no evidence of verbal understanding apart from the word 'no'. His parents were confident that he could hear and recognise ordinary household sounds. His non-verbal abilities were at least normal, and possibly superior.

Distraction tests produced high frequency responses at 40 to 45 dB SPL and low frequency responses at 45 to 50 dB SPL, suggesting a mild persisting hearing difficulty. The grommets were in situ and patent. The parents were advised to speak with deliberate slowness and clarity. At 26 months comprehension was within normal limits, expressive language was only slightly delayed, and distraction tests produced brisk responses at 30 to 35 dB SPL.

Comment

A hearing loss of several months duration at the age when first words are usually spoken might be expected to have a serious affect on language acquisition. It is impossible to be certain that his subsequent progress was attributable to appropriate management, but evidently any deleterious effects of secretory otitis media in this child were entirely reversible.

Case 3. A white girl aged 5½ years had been assessed elsewhere for speech delay and a suspected hearing loss at age 3 years. The parents were told that there was no serious hearing problem, but their description of the hearing test suggested that inappropriate techniques had been used. At age 5½ years she had Reynell scores of 3 years on both expression and comprehension scales. Non-verbal abilities were normal. Pure tone audiometry showed a bilateral conductive hearing loss of 45 to 55 dB and this was confirmed by speech discrimination testing. Her parents confirmed that they had been worried about her hearing for several years. She made rapid postoperative progress, and at age 6½ years was reported to have 'almost normal' language development.

Comment
The history suggests that this girl had had a moderate hearing loss for at least two years. The severity and the duration together probably accounted for her severe language delay, and this hypothesis was supported by her rapid progress after surgery.

Case 4. A white boy aged 3 years 2 months presented because of severe language delay and behaviour problems including aggression, tantrums, and short concentration span. His parents were both in busy full time professional careers and he had been cared for by a succession of at least six au pairs speaking four different languages. He showed no evidence of language or non-verbal skills above the 2 year level. Cooperative hearing tests were impossible, but repeated distraction testing and impedance measurement suggested a variable conductive hearing loss. Secretory otitis media was found at subsequent operation. His mother suspended her career to spend time with him and reported a dramatic improvement after surgery. His progress was excellent, and at age 5 years he was able to enter the reception class of a normal preparatory school.

Comment
It is impossible to determine the relative contributions of secretory otitis media and environmental deprivation to this patient's problems, but an interaction between these two factors is the most plausible explanation.

Case 5. This white girl aged 4 years 2 months was sn elsewhere at age 3 years because of parental concern over hearing and language development. Hearing was said at a local clinic, to be 'within normal limits', but the parents were not satisfied with the child's responses during testing and had disagreed with the clinic's conclusions. At age 4 years 2 months, a Reynell developmental language test indicated a comprehension level of around 2 years 6 months and an expressive language ability of about age 2 years. The non-verbal intelligence quotient (Snijders-Oomen) was 120. Pure tone audiometry showed a bilateral conductive hearing loss of 25 dB. She had evidence of long standing secretory otitis media in the right ear, but there were only minor changes in the left. After surgery she progressed well with intensive speech therapy in a language unit, but at age 5 years 11 months, her Reynell language development scale scores were lower than those normal for her age (comprehension 4·02, expression 4·08, English picture vocabulary scale 2·11).

Comment
This patient's language problem seemed out of proportion to the hearing loss, which was only modest at the time of testing. The unexpectedly slow progress after hearing was restored (compared for example with that of case 3) could be attributed either to the residual effects of a longstanding hearing loss on auditory function (see below) or to an interaction between a hearing loss and a pre-existing 'developmental language disorder'.

Case 6. A black girl aged 3 years 3 months was assessed because she had no speech and no demonstrable understanding of language. Enough non-verbal ability was observed to exclude severe retardation. Cooperative hearing tests showed a 30 to 40 dB hearing loss, and severe secretory otitis media was found at operation. Her family had suffered a series of tragedies and upheavals and her mother was profoundly depressed and socially withdrawn. After surgery her demeanour, play, and hearing in the assessment nursery steadily improved but at least six months elapsed before progress in language was observed. Although her hearing had returned to near normal, a unit for those with partial hearing seemed the most appropriate placement. At age 5 years, her language was still 12 to 18 months behind, but by age 7 years she was ready to return to normal schooling.

Comment
It is likely that this girl's handicap was the product of a similar interaction to that in case 4. As in case 5, there are several possible explanations for the relatively slow progress after surgery. The hearing loss may have led to impairment of auditory perception, or it may have been of no importance at all—the main causative factor may have been her deprivation at home.

Case 7. This white boy aged 2 years 11 months was assessed because he had only three single words and very little understanding of speech. Since the age of

12 months he had suffered frequent ear infections and was a quiet, lethargic child. The Griffiths assessment showed global retardation with scores appropriate for age 2 years in social, non-verbal, and motor areas. Distraction tests produced responses at around 50 to 55 dB SPL, suggesting an appreciable hearing loss. At surgery, thick fluid was found in both ears. After this he became much more lively and began to vocalise and to show evidence of understanding, though six months later he was still showing considerable delay in overall development.

Comment

Serial assessments of this boy's abilities showed evidence of retardation in all areas of development. It seems likely that his intrinsic retardation and placid temperament subtly reduced the number of language interactions to which he was exposed. This unintentional 'secondary' deprivation in combination with secretory otitis media produced severe language delay.

Case 8. This 6 year old white girl had mild spastic diplegia with normal language and intelligence quotient. She had always had a pleasant, extroverted personality. Her mother noted a hearing loss at age 5 years, together with increasing moodiness and a 40 to 50 dB conductive hearing loss was confirmed. This persisted for about eight months before surgery was undertaken, and operation showed obvious secretory otitis media. After surgery an improvement in hearing and mood was noted, but there was no change in her highly competent language abilities.

Comment

Although she had suffered a moderate hearing loss for at least eight months, this had had little effect on her development, presumably because at this age her good intellect and personality enabled her to overcome the disability.

Case 9. A 22 month old white boy was noted to have a hearing loss at a routine medical examination. This was confirmed by distraction tests, which produced no responses to stimuli less than 50 dB SPL. His father reported a recent respiratory infection. He had no other past or present worries about him, and the child was saying a few words. Two months later, hearing responses were normal and the child could perform a toy identification test without difficulty, had normal language development, and otoscopy and impedance were normal.

Comment

The history suggested that in this case the secretory otitis media was associated with the respiratory infection, and the episode was of such brief duration that there was no noticeable effect on language development.

Case 10. This white girl aged 2 years 10 months was thought by her parents to have had impaired hearing since an ear infection three to four months previously. Language development seemed advanced for her age. Pure tone audiogram showed a bilateral 40–45 dB conductive hearing loss and there were obvious signs of secretory otitis media. Four months later the hearing loss had improved to about 30 dB but the otoscopic and impedance findings were essentially unchanged. The parents declined an offer of surgical referral, saying that they spoke clearly because they were aware of the problem and they could see no evidence of any effect on her developmental progress or behaviour.

Comment

In spite of an appreciable hearing loss for at least eight months, this girl's language development seemed unaffected. This may partly be explained by the fact that her language was already well established when she developed secretory otitis media, and perhaps the parents' efforts to speak clearly were also relevant.

Discussion

During the period in which these patients were seen, a much larger number of children who attended for audiological examination was found to have secretory otitis media without any abnormality of language development, and conversely there were many with language problems without evidence of this disorder. Since secretory otitis media is so common, it is difficult in the individual child to determine how much the disorder is affecting development. Parents often report an improvement in the child's hearing immediately after surgery, but it is much more difficult to document subsequent acceleration in language development.

Furthermore, the diagnosis of secretory otitis media with language delay is often followed by several simultaneous interventions in addition to surgery—for example, advice to parents, nursery placement, and beginning speech therapy. In spite of all these difficulties, the patients described above lead us to suspect that secretory otitis media can indeed have a devastating effect on some children, yet be of trivial importance to others. We postulate that at least five variables must be considered to explain these differences. These are:

(1) The age at which the disorder occurs;

(2) The duration of the episodes;
(3) The severity of the hearing loss;
(4) Intrinsic qualities in the child;
(5) The child's environment.

Age of onset. There are both clinical and experimental reasons for the belief that the age of onset is important. Firstly, for obvious reasons, a congenital sensorineural hearing loss has much more devastating effects on language development than a hearing loss of similar magnitude acquired after the child has learned to talk. It is reasonable to assume that the same would apply to the conductive loss caused by secretory otitis media. Secondly, there is now overwhelming evidence that the infant learns a great deal about discrimination and production of speech sounds in the first year of life and this learning is an essential prerequisite for spoken language.[8] The diminished quantity and range of babble and jargon noted in cases 1 and 2 suggests that secretory otitis media could have a considerable effect on this vital period of development. Thirdly, we suspect, but cannot at this stage confirm, that in longstanding secretory otitis media the ability to discriminate complex sounds such as speech may recover more slowly after surgery than does the ability to perceive pure tones as used in audiometry. This hypothesis is one of several possible explanations for the slow progress observed in cases 5 and 6 after surgery. There may be a neurophysiological explanation for these observations: it is known that normal visual stimulation is needed for the development of the visual pathways, and there is some evidence that the same is true for auditory development.[9 10] If this is so, then secretory otitis media in infancy may well cause the auditory equivalent of 'amblyopia'. We can only speculate about the age range within which this might happen but it is an issue of particular importance because of the seemingly raised prevalence of secretory otitis media in preterm infants.

Duration. The duration of episodes of secretory otitis media is very variable and is often impossible to assess. It seems obvious that the most serious effects will be seen in those children who have prolonged or continuous attacks without remission. These children can sometimes be recognised by reference to previous audiological tests (provided these were competently performed) or by parental observation. There was evidence in our cases 1 and 2 that the disorder had been present for at least six months and for 12 to 24 months in cases 3 and 5. Conversely, in cases 9 and 10, spontaneous improvement after two to three months was observed.

Severity of hearing loss. The severity of the hearing loss is also unpredictable and varies from day to day. The reasons for this variability are not entirely clear, but probably the volume of the effusion and the degree of negative pressure in the middle ear are more important than the viscosity of the effusion.[11] It seems entirely logical to suggest that the extent of the hearing loss is an important factor in determining its effects on development, but this is difficult to confirm, firstly because hearing testing techniques in infancy do not define precise thresholds and secondly because a single test tells us nothing about the day to day variations. Furthermore, some young children with secretory otitis media (for example case 1) seem to have a rather more severe hearing loss than one would normally expect to find in patients with conductive deafness, possibly due to the 'amblyopia-like' effect postulated above. In most of our reported patients, the hearing loss seemed to be at least 30 dB in magnitude, although in case 3, it was only 25 dB. All these children had bilateral secretory otitis media which of course is likely to have far more serious effects than unilateral disease.

Factors in the child. Intrinsic differences between children in intelligence and temperament are also likely to interact with a hearing loss. One would expect the intelligent, extroverted child to seek communication more actively and to make more effort to comprehend sound than one who is placid or dull. The most serious effects probably occur when secretory otitis media coexists with global retardation, as exemplified by case 7, though our experience with case 4 suggests that the effects on behaviour and concentration may cause a spurious reduction of non-verbal as well as verbal skills during formal assessment.

Effect of environment. Lastly, it would be surprising if environmental factors did not also contribute. There are wide variations in children's exposure to constructive linguistic experiences[12] and in cases 4 and 6, there was good reason to suspect that this was seriously deficient. Conversely in cases 8 and 10 the child was probably exposed to a very stimulating environment. The amount of conversation between parent and child in close physical proximity, the effects of prolonged background noise, and perhaps the natural intensity and clarity of the parents' speech may also be important. Substantial differences in linguistic environment are found between families, independent of social class,[13] and it is clear that social class cannot be a satisfactory measure of the language stimulation to which a child is exposed at home.

Conclusion. We recognise that our observations may have other explanations and that we are applying a certain circularity of argument. Nevertheless, the idea that secretory otitis media can be related to developmental problems is by no means new; many of the ideas outlined here have been mentioned individually in other publications, but do not seem to have been brought together as a single working hypothesis in any research study.

Most studies have shown a statistically significant correlation between middle ear disease and learning problems but the magnitude of the effect is surprisingly small and might be regarded as unimportant in practice. We suggest that in certain children secretory otitis media has a very substantial effect on development, but that in research studies this effect is diluted by the inclusion of many children in whom the disorder is of brief duration and trivial importance.

Our clinical experience suggests that research designs that simply compare linguistic or developmental outcomes in children with and without middle ear disease are unlikely to be profitable.[5] [7] Studies on the effects of secretory otitis media on language development must be prospective and longitudinal, and must incorporate data on the changes in hearing and middle ear status over time, the linguistic and social environment, and the temperament and non-verbal skills of the child. A project of this magnitude is expensive but investment in detection and treatment of secretory otitis media is massive,[14] and further research to confirm or refute our hypothesis is urgently needed.

If our hypothesis is wholly or even partly correct, there are important clinical implications. The clinician cannot be content with the diagnosis of a hearing loss caused by secretory otitis media, since the other factors discussed here must also be considered. It follows that secretory otitis media is not invariably an indication for surgery, particularly as the long term benefits are still uncertain. Although careful assessment of these children is essential, it is still far from universal.

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Growth and somatomedin responses to growth hormone in Down's syndrome

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SUMMARY Five growth retarded children with Down's syndrome, three girls and two boys aged between 3½ and 6½ years with trisomy 21, were treated with human growth hormone for six months. Before treatment the growth hormone response to sleep and insulin-arginine load, as well as serum concentrations of insulin, thyroid hormones, and cortisol was found to be in the normal range. During the treatment with human growth hormone the growth velocity increased in all the children with Down's syndrome from 2·3–2·8 cm to 3·3–5·8 cm per six months. The serum concentrations of immunoreactive insulin like growth factor 1 (IGF-1) were low before treatment and increased during the treatment with human growth hormone. The serum concentrations of immunoreactive insulin like growth factor 2 (IGF-2), which were within the normal range, however, increased during treatment with human growth hormone. Children with Down's syndrome respond to treatment with human growth hormone, with an increase in both growth velocity and serum somatomedin concentrations.

Growth retardation and development of presenile dementia are characteristic features of Down's syndrome. Even if the basic defect, trisomy for chromosome 21, is well defined, little is known about the mechanisms causing growth retardation, mental retardation, and the other abnormalities.

Somatomedins have been proposed as regulating growth, including brain growth,[1] and being altered in mental retardation due to disturbances in brain development.[2] Several studies have examined the role of somatomedins in Down's syndrome.[3–5] Patients with Down's syndrome show a deficiency in serum insulin like growth factor 1 (IGF-1). This growth hormone dependent somatomedin fails to rise during childhood and remains at a low concentration throughout life.[3] The serum concentration of insulin like growth factor 2 (IGF-2) in patients with Down's syndrome is, however, within the normal range,[5] and the receptors for somatomedins and insulin in fetuses with Down's syndrome have been found to be normal.[4] Determination of serum somatomedins by a radioreceptorassay proposed to detect a fetal form of somatomedin showed scarcely detectable concentrations in fetuses with Down's syndrome,[6] but raised concentrations throughout postnatal life.[3] A delayed maturation and incomplete switching from production of a fetal form of somatomedin to the IGF-1 regulated by growth hormone was suggested in patients with Down's syndrome.

Growth becomes dependent on growth hormone during the first year of life. At this time growth hormone begins to regulate the production of somatomedin.[7] The concentration of growth hormone has been reported to be in the normal range in patients with Down's syndrome.[8] Some trials with treatment with growth hormone in patients with Down's syndrome have been performed. However, these studies used animal growth hormone and even a peroral route for administration, and thus the results are inconclusive.[9] The current belief therefore is that children with Down's syndrome do not respond to human growth hormone.

The aim of this investigation was to study if somatomedin concentrations, especially IGF-1, and growth velocity in children with Down's syndrome substantially increased on treatment with standard dosages of parenterally given human growth hormone.

Methods

Subjects (Table 1). Five children, three girls and two boys of ages 3½ and 6½ years with trisomy 21, but without clinically important congenital malformation, were chosen. None were malnourished or had any deviation in dietary habit or food preferences. They were all cared for by their biological parents. None of them had had any severe infectious disease or had been taking any drug during the last year before or during the treatment with human growth hormone. All had profound growth retardation with a height >3 SD below the mean according to the Swedish standard,[10] but they did not deviate further from the −3 SD channel of the growth chart the last year before treatment. The parents were all of normal height, except for the mother of case 4, who was 1·50 m.

Laboratory investigations before treatment with human growth hormone. Glucose clearance after intravenous glucose load (0·3 g/kg birthweight) was within the normal range in all cases (half life 28–54 minutes). Thyroid hormone assays (thyroid stimulating hormone, triiodothyronine, and thyroxine) were all within normal reference limits. Plasma cortisol concentration was measured after insulin stimulation and was found to be within normal limits in all cases (660–1100 nmol/l (23·9–39–8 μg/100 ml)).

Concentrations of immunoreactive growth hormone were determined by a radioimmunosorbent technique[11] using human pituitary growth hormone (Kabi AB, Stockholm) for labelling and rabbit antihuman pituitary growth hormone. The results were expressed in μg/l using the World Health Organisation International Reference Preparation of Growth Hormone, 66/217, as a reference.[11] The secretion of growth hormone was evaluated during sleep and after an arginine-insulin load. Four of the children showed a peak value of at least 16 μg/l in one of the tests; case 4 had a maximal peak value of 8·8 μg/l (Table 2).

Somatomedin assays. The concentrations of somatomedins were determined by two radioimmunoassays. The radioimmunoassay for IGF-1, which allows determination in whole serum, has been described previously.[12] This assay measures predominantly IGF-1, and IGF-2 crossreacts only 1%. The arbitrary local reference serum used as standard contained 180 ng of IGF-1/ml.

The radioimmunoassay for IGF-2, with sepharose coupled antibodies and pure IGF-2 as ligand was used.[13] The crossreaction of IGF-1 varied between 8 and 10%. The immunoreactive IGF-2 values are given for acid ethanol extracted serum. The results are expressed in ng equivalents of IGF-2 and corrected for the crossreaction of IGF-1. The

Table 1 *Clinical characteristics of five children with Down's syndrome with growth retardation, before and after six months' treatment with 0·5 U/kg/week of human growth hormone*

Case no	*Before or after treatment*	*Sex*	*Age (yrs, months)*	*Skeletal age (Greulich-Pyle) (yrs)*	*Weight (kg)*	*Height (m)*	*Height (Swedish standard) (SD)*	*Growth over six months (10^{-2} m)*	*Mental development (Griffiths' scale) (quotients)*
1	Before	F	6·6	4·5	14·7	0·952	−5·0	2·8	34
	After		7·1	5·0	15·3	1·001	−4·0	5·1	34
2	Before	M	5·0	3·5	13·5	0·930	−4·0	2·5	60
	After		5·5	4·0	14·5	0·972	−3·5	4·3	60
3	Before	F	5·6	3·0	18·0	0·978	−4·0	2·8	40
	After		6·1	3·5	18·0	1·010	−3·5	4·2	40
4	Before	M	4·1	3·5	15·4	0·873	−4·0	2·3	52
	After		4·6	4·5	15·4	0·909	−4·0	3·6	55
5	Before	F	3·4	2·0	13·4	0·870	−3·0	2·3	59
	After		3·9	2·5	15·2	0·928	−1·5	5·8	60

Table 2 *Concentrations of plasma growth hormone (μg/l) during sleep and the insulin-arginine loading test in five patients with Down's syndrome, before treatment with growth hormone*

Case no	*Sleep test Time (mins)*					*Insulin-arginine loading test Time (mins)*						
	0	*30*	*60*	*90*	*120*	*0*	*30*	*60*	*90*	*120*	*150*	*180*
1	55·0	25·0	12·4	4·8	9·3	2·3	3·2	16·7	6·4	13·8	16·5	13·0
2	16·7	6·4	3·3	1·7	2·7	4·2	1·5	1·9	3·3	9·7	13·7	13·2
3	5·2	2·2	3·5	1·5		2·1	7·1	1·4	9·5	12·3	11·4	19·9
4		6·2	8·8	8·6	5·4		1·9	4·4	5·4	3·4		
5		9·6	4·7	2·7	6·0	11·8	5·7	11·8	18·4	7·9	16·5	20·0

arbitrary local reference serum used as standard was shown to contain 980 ng of IGF-2/ml after correction for its content of IGF-1.

Growth hormone loading test. A daily dose of 0·08 U/kg body weight of human growth hormone (Crescormon, KabiVitrum) was administered subcutaneously at 1900 during 10 days in hospital, according to Rudman *et al.*[14] Serum immunoreactive IGF-1 and IGF-2 concentrations were determined by radioimmunoassay on 0, 5, and 10 days of the human growth hormone loading test. All serum samples were immediately frozen at −20°C until assayed.

Growth hormone treatment. After the human growth hormone loading test the children with Down's syndrome were treated at home with 0·5 U/kg week of human growth hormone (Crescormon, KabiVitrum), divided into three doses given at bedtime. Height and weight measurements were performed monthly by the same physician, and the average of three readings was recorded at each visit. Height was measured on a Stadiometer mounted on a wall. Blood samples for somatomedin assays were drawn once monthly between 0930 and 1100. Before and after the six months of treatment with human growth hormone, examinations of the mental development according to Griffiths' mental development scale[15] and of the skeletal maturation according to the method of Greulich and Pyle[16] were performed.

Results were expressed as mean±1 standard deviation (SD). Because of the small number of patients no significance test was performed.

Results

Growth and development. All the patients increased their growth velocity during treatment with human growth hormone (Table 1). The increase of the growth velocity ranged from roughly 50% to 200%. The growth velocity during treatment ranged between 3·3 and 5·8 cm each six months (mean (SD) 4·5 (1·0) cm) compared with 2·3–2·8 cm (2·5 (0·3) cm) before treatment and 1·5–4·0 cm (2·6 (1·0) cm) after treatment (Fig. 1). The skeletal maturation of the children with Down's syndrome was retarded by about one and a half years, according to the method of Greulich and Pyle,[16] both before and after treatment with human growth hormone (Table 1). Quotients according to Griffiths' mental development scale[15] before and after treatment with human growth hormone did not show any differences.

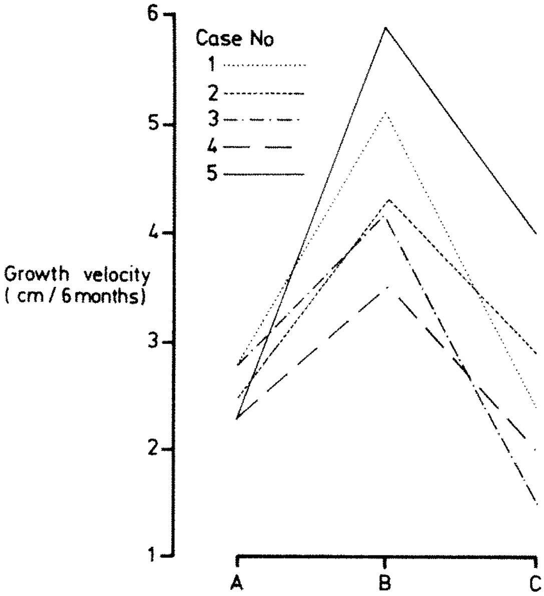

Fig. 1 *Growth (cm) during six month periods in five children with Down's syndrome (A) before; (B) during; and (C) after six months' treatment with 0·5 U/kg/week human growth hormone.*

Serum somatomedins. In all the patients the serum concentration of immunoreactive IGF-1 increased during the ten days of loading with human growth hormone (Fig. 2). The increase from concentration before treatment ranged from 46% to 234%. Concentrations before treatment (62·3 (17·5) ng/ml) were low and ranged between −2 and −1 SD below the normal concentration in children of this age (2–4 years: 121 (38) ng/ml; 4–6 years: 126 (64) ng/ml).[17] The mean immunoreactive IGF-1 concentration increased to normal (125·6 (48·3) ng/ml) after 10 days of treatment and ranged from −1 to +1·5 SD of the control value. During the six months of treatment with human growth hormone the concentrations remained above that before treatment in all patients (Fig. 3). The increases in serum immunoreactive IGF-1 concentrations six months after the start of treatment with human growth hormone ranged from 37% to 224% of the concentrations before treatment. The maximal concentration during treatment of one patient (case 5) was even greater than +3 SD above mean for age.

In all patients the serum concentrations of immunoreactive IGF-2 increased during the loading test (Fig. 2). The increases from values before treatment ranged from 30% to 108%. Concentrations before treatment lay between −2 SD and −1 SD below the mean in normal adults (606 (158) ng/ml[13]) and after 10 days of treatment between −1

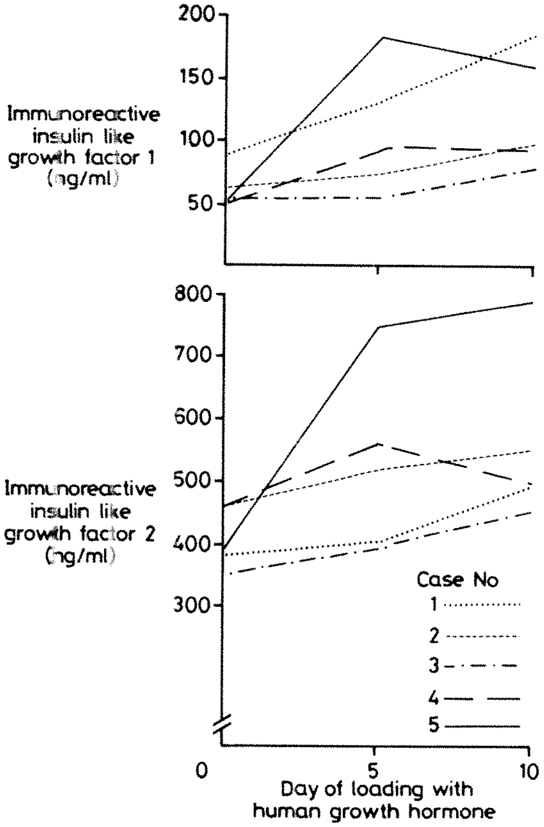

Fig. 2 *Serum somatomedins (ng/ml) determined by radioimmunoassays for IGF-1 (upper panel) and IGF-2 (lower panel) during 10 days of human growth hormone loading (0·08 U/kg/day) in five children with Down's syndrome. Serum immunoreactive IGF-1 and IGF-2 concentrations were determined on 0, 5, and 10 days of the human growth hormone loading test.*

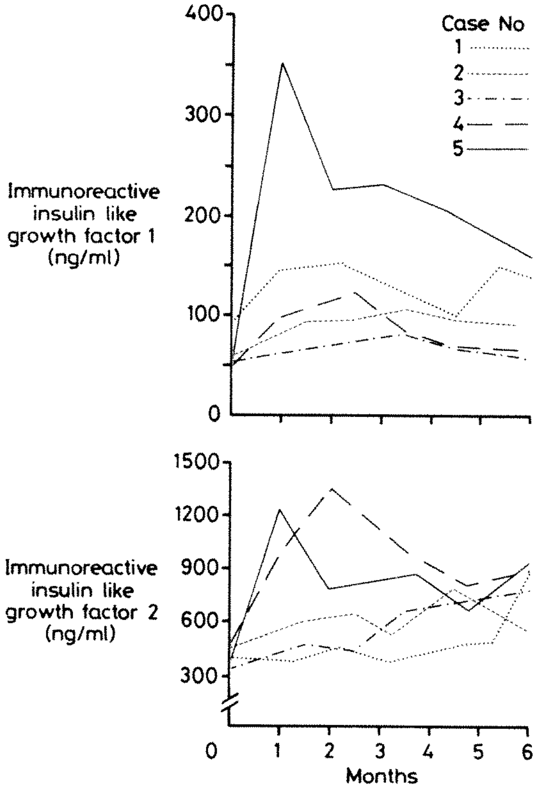

Fig. 3 *Serum somatomedins (ng/ml) determined by radioimmunoassays of IGF-1 (upper panel) and IGF-2 (lower panel) during six months' treatment with 0·5 U/kg/week human growth hormone in five children with Down's syndrome. Serum immunoreactive IGF-1 and IGF-2 concentrations were determined monthly from months 0–6 of treatment.*

and +1·5 SD. The immunoreactive IGF-2 concentrations remained raised during treatment (Fig. 3), and in two patients (cases 4 and 5) the maximum concentrations during treatment were increased to more than +3 SD from normal. The increases in serum immunoreactive IGF-2 concentrations at the end of the six months' treatment with human growth hormone ranged between 15% and 176% of the concentrations before treatment.

There were great individual variations both in the time of occurrence of the peaks and in the magnitude of immunoreactive IGF-1 and IGF-2 responses to treatment with human growth hormone (Fig. 3). Comparison of individual responses (Figs. 1 and 3) showed a relation between maximal responses of immunoreactive IGF-1 and increase in growth velocity.

Discussion

Earlier studies have shown that, similar to pygmies,[18] children with Down's syndrome have a selective deficiency of serum IGF-1 concentrations.[3 5] From the present results it is clear that children with Down's syndrome respond to treatment with human growth hormone. The growth velocity increased considerably during the six months of treatment in all the patients. This is remarkable, as the growth velocity before treatment was within the normal range for healthy children at this age and height. Skeletal retardation was observed in the present patients. There was no difference between the skeletal retardation before and after treatment, crudely indicating that no acceleration of the maturation accompanied the growth spurt. The concentrations of the IGF-1 like peptide determined by radioimmunoassay were low before treatment in all the patients and increased after 10 days of loading with human growth hormone to normal for this age group. Although the IGF-2 values were within the normal range, immunoreactive IGF-2 concentrations also increased promptly on treatment. The individual increases in these children with Down's syndrome suggested a relation between growth velocity and the growth hormone dependent somatomedin IGF-1.

Although the present findings suggest deficiency of growth hormone, children with Down's syndrome seem to have reasonable endogenous growth hormone concentrations, as evaluated from two accepted clinical standard test procedures in the present patients, as well as from earlier reports.[8] Hayek and Peake[19] classified children with short stature into three groups. Group 1 comprised the children deficient in growth hormone and groups 2 and 3 both comprised children with normal serum growth hormone concentrations and low somatomedin C (IGF-1) concentrations. The children of group 2 responded with increased velocity of growth and increased concentrations of somatomedin treatment with human growth hormone, while the children of group 3—that is, the Laron dwarfs—with a growth hormone receptor failure[20] did not respond at all. Patients with Down's syndrome, thus, could be classified in group 2. Before a partial growth hormone insufficiency can be eliminated in patients with Down's syndrome, however, further studies will be required to determine their pattern of secretion of growth hormone over 24 hours to evaluate a possible 'relative' growth hormone deficiency.

This study shows that children with Down's syndrome increase their growth velocity during six months' treatment with human growth hormone, but does by no means prove that short term (or long term) treatment with human growth hormone increases final height in these children. Even if the delay in skeletal maturation during the six months was unchanged, it has to be considered that skeletal maturation as measured by most routine methods is very crude, while in the long run increased growth and maturation could well be parallel. After treatment growth velocity essentially returned to values before treatment.

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Gonadal function after testicular radiation for acute lymphoblastic leukaemia

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SUMMARY Pubertal maturation, growth, and gonadal function were assessed in 13 boys with acute lymphoblastic leukaemia who had received direct testicular irradiation three to nine years earlier as treatment for testicular relapse or prophylaxis against this complication. Six boys had reached Tanner stage III–V puberty, five of whom had normal growth velocities and bone ages equivalent to chronological age. One boy exhibited maturational arrest on entering stage IV. The remaining seven children (54%) showed evidence of complete pubertal delay or arrested development in stage II, with absence of the pubertal growth spurt and often with delayed bone age. Basal gonadotrophins were abnormally high in all 13 boys, and those with delayed puberty had prepubertal concentrations of testosterone.

Testicular irradiation given before puberty causes permanent Leydig cell damage in a high proportion of subjects, necessitating testosterone supplementation. The extent of damage may be related to the age at which radiation is delivered.

As treatment of acute lymphoblastic leukaemia has led to prolonged survival, testicular relapse has become more common, usually occurring within two years of stopping treatment.[1] As this complication is potentially curable when treated with further intensive chemotherapy and local testicular irradiation, the long term effects of treatment become important.

We recently reported that testicular irradiation in 11 prepubertal boys with acute lymphoblastic leukaemia caused severe Leydig cell damage, as shown by an appreciable decline in the plasma testosterone response to human chorionic gonadotrophin stimulation, six months after radiotherapy.[2] Brauner *et al* found similar changes in 12 patients who had received local testicular irradiation 10 months to 8½ years earlier.[3]

The purpose of this study was to assess pubertal maturation and gonadal function in 13 boys who had received previous testicular irradiation, thus enabling us to ascertain whether Leydig cell damage in these patients is permanent or whether there is capacity for recovery.

Patients and methods

Between 1974 and 1982, 20 boys with acute lymphoblastic leukaemia developed testicular relapses (found on biopsy) and were treated by local radiation and chemotherapy. Unilateral orchidectomy was also performed in two early cases before standardisation of treatment. A further two boys had prophylactic testicular irradiation as part of the UKALL VI protocol. All patients were prepubertal at the time of radiotherapy. Nine of the 22 boys were excluded either because they were less than 10 years of age or had died, leaving 13 available for assessment. Seven of these were included in our previous study using the human chorionic gonadotrophin test.[2]

Table 1 shows clinical and treatment data, including details of radiation, in these 13 boys. Eleven had received 24 Gy of radiation to the testes in 10 fractions, accompanied by a reinduction and consolidation regimen consisting of vincristine, prednisolone, asparaginase, cyclophosphamide, cystosine arabinoside, and, in some, daunorubicin. Ten had completed treatment and one was still receiving standard maintenance therapy at the time of the study. This consisted of 6-mercaptopurine, methotrexate, vincristine, and prednisolone. One boy (patient 12) had received two courses of irradiation to a total dose of 36 Gy. One further boy (patient 11) received 15 Gy of prophylactic testicular

Table 1 *Initial chemotherapy protocol, relapse status, and radiation data on 13 boys with acute lymphoblastic leukaemia receiving testicular irradiation*

Patient no	*Initial treatment protocol*	*Relapses*	*Age at irradiation (years)*	*Interval between testicular irradiation and study (yrs)*	*Dosage testicular irradiation (Gy)*	*Dosage cranial irradiation (Gy)*
1	IV	T	8·9	4·9	24	24
2	VI	CNS+BM	10·6	4·8	15	24+24 CrSp
3	II	T+CNS+BM	9·7	7·6	24	24+24 CrSp
4	V	T*	11·0	5·1	24	24
5	UKCCSG	T	11·9	3·3	24	24
6	V	T	7·6	5·6	24	24
7	V	T	9·6	4·7	24	24
8	GOS	T+CNS+BM	7·6	5·5	24	24+24 CrSp
9	V	T	8·4	4·6	24	24
10	II	T	6·4	6·2	24	24
11	V	T	8·7	8·7	24	24
12	III	T*	5·5+9·3	8·4+4·6	36	24
13	III	T+CNS+BM	9·7	3·2	24	24+24 CrSp

*Patients with single testis.
CrSp=craniospinal; T=testicular; CNS=central nervous system; BM=bone marrow.
Protocols II and III contain cyclophosphamide±adriamycin in addition to 6-mercaptopurine, methotrexate, vincristine, cytosine arabinoside, and prednisolone.
UKCCSG T cell protocol contains thioguanine, CCNU in addition to above.

irradiation and was still on treatment. Before testicular relapse all patients had been treated using standard chemotherapy protocols and cranial prophylaxis comprising 24 Gy cranial irradiation and intrathecal methotrexate (Table 1). Four boys had received a second course of craniospinal irradiation and prolonged treatment with intrathecal methotrexate for central nervous system relapse (Table 1).

All patients were assessed regularly as outpatients with respect to growth velocity and pubertal progression (Tanner).[4] As testicular growth is impaired after irradiation,[3] testicular volume could not be used as an index of pubertal development and penile growth, scrotal rugosity, and distribution of pubic hair were the parameters used.

Basal values for plasma testosterone luteinising hormone, and follicle stimulating hormone were measured by radioimmunoassay. Bone age was estimated by the method of Greulich and Pyle.[5]

Results

Clinical findings. The findings for pubertal status and growth velocity are summarised in Table 2, which also gives the results for bone age, plasma testosterone, plasma luteinising hormone, and follicle stimulating hormone.

Six boys aged 13·3 to 17·3 years at the time of the study showed stage III–V pubertal development. One of the six received 15 Gy prophylactic irradia-

Table 2 *Growth data, pubertal status, and biochemical data including plasma testosterone, luteinising hormone (LH), and follicle stimulating hormone (FSH) on 13 boys with acute lymphoblastic leukaemia after testicular irradiation*

Tanner stage	*Patient no*	*Chronological age (yrs)*	*Bone age (yrs)*	*Height velocity (cm/yr)*	*Puberty stage genitalia*	*FSH (U/l)*	*LH (U/l)*	*Testosterone (nmol/l)*
Stage III–V	1	13·8	14	8	III	>40	25·5	3·5
	2	15·4	15	8	IV	12·0	7·3	12·0
	3	17·3	16–17	6	IV	>40	20·9	15·5
	4	16·1	16	9	V	>40	35·7	6·8
	5	15·2	15–16	2	IV	36	28·4	14·5
	6	13·3	13·5	7	IV	12·2	9·3	4·8
Stage II	7	14·2	10–11	3	II	34·2	24·0	0·9
	8	13·0	10	2·5	II	34·7	23·0	1·3
Stage I	9	13·0	13·5	4	I	>40	21·1	1·9
	10	12·6	12·5	3	I	32·6	21·9	0·5
	11	14·2	13	2·5	I	34·2	20·2	1·6
	12	13·9	12·6	3	I	>40	20·0	1·3
	13	12·9	10–11	1·5	I	31·9	21·5	1·5

tion at the age of 10·6 years and the remainder had 24 Gy at an average age of 9·8 years (range 7·6 to 11·9 years). One had had a unilateral orchidectomy. Five of the six had shown a normal adolescent growth spurt and had normal bone ages. One boy had remained in stage IV puberty for 19 months and had failed to show adolescent acceleration of growth. His bone age was also normal.

Two boys aged 13 years and 14·2 years showed early pubertal changes (stage II) with some penile growth; one had scant pubic hair. Neither boy had shown progression in his pubertal development or acceleration of growth over the previous 12 months. Bone age was delayed by three to four years in both boys. These two patients were irradiated at the ages of 7·6 and 9·6 years respectively.

Five boys aged 12·6 years to 14·2 years showed no evidence of pubertal development or accelerated adolescent growth. Bone age was delayed by 1·2 years to 1·9 years in three of them. These patients received testicular irradiation at a mean age of 7·8 years (range 5·5 to 9·7 years), while one of them had a second course of irradiation (total dose 36 Gy) and unilateral orchidectomy.

Puberty stage *versus* age at irradiation was subjected to linear regression analysis (Figure).

Endocrine findings. All the patients showed raised basal follicle stimulating hormone values ranging from 12·2 U/l to over 40 U/l. Basal values in normal boys of this age are usually less than 7·8 U/l. In addition, basal concentrations of luteinising hormone were greater than 20 U/l in all but two boys, both of whom had shown pubertal progression. Normal values for luteinising hormone at this age are usually less than 3·3 U/l.

In the five boys with normal progression, basal testosterone values ranged from 3·5 nmol/l to 15·5 nmol/l (mean 8·5 nmol/l). The one boy in whom puberty seemed to have been arrested in stage IV had a plasma testosterone value of 14·5 nmol/l. The two boys with slight pubertal development had basal plasma testosterone values of 0·9 and 1·3 nmol/l. These values are in the normal prepubertal range. The five boys with no evidence of pubertal development had basal plasma testosterone values between 0·5 nmol/l and 1·9 nmol/l.

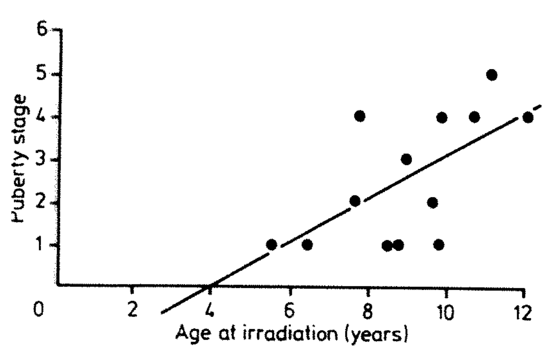

Figure *Regression analysis of the puberty stage and age at irradiation.*

Puberty stage = 0·5 (age at irradiation) − 2·1 (r = 0·63; P = 0·02).

Five of the seven children previously studied six months after irradiation (patients 1 and 6 to 11) and found to have poor plasma testosterone responses to human chorionic gonadotrophin stimulation continued to show abnormally low peak plasma testosterone values (less than 2 nmol/l) when tested two to four years later. These five patients (patients 7 to 11) subsequently exhibited pubertal delay and growth failure. The remaining two boys (patients 1 and 6) showed recovery of testicular function two and three years after irradiation with peak plasma testosterone values of 4·6 nmol/l and 6·8 nmol/l respectively. They have exhibited normal virilisation and adolescent growth.

Discussion

Endocrine disturbance seems to be relatively uncommon in patients who receive uncomplicated treatment for acute lymphoblastic leukaemia. Growth hormone deficiency assessed by conventional stimuli after prophylactic cranial irradiation is rare, but becomes frequent with increasing radiation dosage.[6] A normal growth pattern, however, is often preserved despite biochemical abnormalities.[7] Gonadotrophin deficiency is not usually found,[6] but abnormalities of thyroid stimulating hormone and corticotrophin secretion have been reported without clinical evidence of endocrine disorder.[6] Although standard chemotherapy consisting of vincristine, prednisolone, 6-mercaptopurine, and methotrexate reduces the number of germ cells of the testis as measured by the tubular fertility index,[8] Leydig cell function seems to remain intact,[9] and most boys undergo normal virilisation.[10] Cytosine arabinoside and cyclophosphamide further reduce the tubular fertility index[8] but do not impair testosterone secretion.[9]

This picture seems to be changing with the treatment of testicular relapse. It is evident from our results that the Leydig cell sustains severe and often permanent damage after fractionated testicular radiotherapy, shown by complete failure of virilisation in five boys and by arrest of pubertal growth and development in a further three (two in stage II and one in stage IV). All but one of these boys had received 24 Gy of local irradiation, while the other had received a total dose of 36 Gy to his remaining testicle after orchidectomy. Of the five patients showing normal progression, one had received a lower dose of 15 Gy for prophylaxis, while the others had received the standard treatment dose of 24 Gy. They attained stage II puberty at a mean of 12·7 years.

Damage to the Leydig cell was suspected in our previous study when we found impaired testosterone responses to human chorionic gonadotrophin six months after radiotherapy.[2] In two of the seven boys common to both studies, recovery of function was found when repeat human chorionic gonadotrophin tests were performed two to four years later. This has subsequently been corroborated by the finding of normal pubertal progression in these two boys, while testosterone responses to human chorionic gonadotrophin remained impaired in the five others who failed to mature.

The absolute dose of radiation at which recovery of the Leydig cell does not occur is unknown. It would seem to be greater than 24 Gy, and may be dependent on the age at which irradiation is given. It is of interest that boys showing normal adolescent development received testicular radiotherapy at a mean age of 9·8 years compared with 7·9 years in those progressing no further than stage II. Although we cannot draw any firm conclusions from this, it strongly suggests that there may be a greater risk of permanent Leydig cell failure if radiation is given during early childhood. Linear regression analysis confirms this impression. This point is well illustrated by the boy who received 24 Gy of local radiotherapy at 11 years of age, and despite unilateral orchidectomy exhibited normal pubertal maturation.

Adequate pubertal concentrations of testosterone have only been achieved in those successfully undergoing virilisation by virtue of a compensatory rise in luteinising hormone to abnormal values. All of those exhibiting little or no spontaneous development had testosterone concentrations in the prepubertal range. Both gonadotrophins reached abnormally high values in this group of patients excluding a diagnosis of 'simple delay' or radiation induced pituitary failure. Growth hormone deficiency was also ruled out in the two boys treated for meningeal leukaemia with a second course of cranial irradiation, showing abnormal growth patterns.

In conclusion, not only does testicular irradiation cause germ cell damage and subsequent sterility, but there is a considerable risk that it will impair Leydig cell function and that testosterone replacement treatment will be required to achieve virilisation at the normal time of adolescence. Nonetheless in a minority of children, Leydig cell recovery occurs sufficiently to allow pubertal progression and this may be related to the age at which radiotherapy is given. These findings emphasise the need for vigilant long term follow up of all patients treated with local testicular radiotherapy. If testosterone replacement is found to be necessary it is advisable to start treatment before these boys suffer further psychological trauma through short stature and immature development. Thirteen to 14 years of age seems to be a suitable time in most cases, although individual needs should always be taken into account.

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Response to ACTH in the newborn

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SUMMARY Adrenocortical function was studied in 52 newborn infants who had been divided into three groups: preterm well, preterm ill, and term ill. Basal plasma 17-hydroxyprogesterone concentrations were significantly increased in both groups of preterm infants. There was no significant difference in basal plasma cortisol concentrations, although they were highest in preterm ill infants. All infants responded to adrenocorticotrophic hormone (ACTH) stimulation (36 µg/kg intramuscularly) with a two to threefold increase in the concentration of both steroids. The peak plasma 17-hydroxyprogesterone response was significantly higher in preterm ill infants. A subgroup of five infants, who were highly stressed but had undetectable basal plasma cortisol concentrations, also showed an appropriate response to ACTH. The results provide useful reference data to assess adrenal function in the infant of a mother given glucocorticoids during pregnancy. There is also a change from the pattern of fetal adrenal steroidogenesis soon after birth, which may be affected by exogenous ACTH stimulation. Roughly 10% of stressed newborns failed to synthesise cortisol basally; temporary glucocorticoid replacement for such infants may be appropriate.

Plasma concentrations of 17-hydroxyprogesterone are markedly raised in untreated infants with congenital adrenal hyperplasia due to 21-hydroxylase deficiency.[1-3] In a recent study, concentrations of this steroid were also shown to be appreciably higher in stressed, ill newborn infants compared with healthy term infants.[4] In some ill preterm infants plasma concentrations of 17-hydroxyprogesterone were as high as 100 nmol/l (30·1 ng/ml). Concomitant measurement of plasma cortisol concentrations, however, showed no correlation with the plasma 17-hydroxyprogesterone values. In about 10% of ill infants cortisol concentrations were undetectable (<28 nmol/l (<1 µg/100 ml)).

Previous studies of adrenal function in newborn infants report variable plasma cortisol concentrations during the first week of life in infants.[5-9] In general, basal plasma concentrations of cortisol exceed 100 nmol/l (3·6 µg/100 ml). Less information is available on cortisol values in preterm infants, particularly those who are stressed.[10] This paper reports a systematic study of adrenocortical function in both preterm and term stressed infants. The plasma 17-hydroxyprogesterone and cortisol response to short term exogenous adrenocorticotrophic hormone (ACTH) stimulation is also reported. The results provide useful reference data to assess neonatal adrenal function after administration of glucocorticoid during gestation.

Patients and methods

Fifty two infants born in the maternity department of the University Hospital of Wales were studied. They were classified into three groups: preterm ill, preterm well, and term ill. The clinical assessment of seriously ill infants was the criterion used to identify those who were stressed. These infants had a variety of conditions, including respiratory problems requiring ventilation, perinatal asphyxia, septicaemia, and major neonatal surgery. Gestational age was assessed by the method of Ballard *et al.*[11] The plasma 17-hydroxyprogesterone and cortisol response to ACTH stimulation was performed either on the third or fourth day after birth. Capillary blood samples were collected before and one hour after an intramuscular injection of Synacthen (Ciba). The dose used was 36 µg/kg body weight in a volume ranging from 0·2–0·5 ml. Informed parental consent was obtained in each case and the study was approved by the hospital ethics committee.

Plasma concentrations of 17-hydroxyprogesterone[12] and cortisol[13] were determined by radioimmunoassays using a ^{125}I-radioligand and antisera coupled to solid phase supports. The volume of plasma required to perform both assays in duplicate was 140 µl. Significant cross reactivity of the cortisol antiserum was observed for 21-deoxycortisol (65%) and prednisolone (6·9%). For the 17-hydroxyprogesterone antiserum the cross reactivity with progesterone and 17-hydroxypregnenolone was 5·9% and 7·4%, respectively.

Statistical analyses of the 17-hydroxyprogesterone and cortisol data were performed using log transformation and the F test.

When comparing values before and after administration of Synacthen analysis of covariance was used to adjust for the differences in the values before administration.

Results

Table 1 shows the clinical details of the 52 infants studied. As expected, preterm infants who were ill had lower birth weights and gestational ages. The values for the group were not significantly different. Table 2 and Figure 1 summarise basal and peak plasma cortisol and 17-hydroxyprogesterone responses to ACTH stimulation in each of the three groups of infants.

The mean basal plasma cortisol concentration was highest in the group of preterm ill infants, but the difference was not significant. Basal plasma 17-hydroxyprogesterone concentrations were significantly higher in both groups of preterm infants ($p<0·05$). Term ill infants had 17-hydroxyprogesterone concentrations similar to their healthy counterparts.[3] In a more recent study of 17-hydroxyprogesterone concentrations determined in filter paper blood spots obtained from 100 healthy term infants, the mean (SD) concentration was 7·5 (2·3) nmol/l (2·3 (0·71) ng/ml) (unpublished observations). All infants responded to ACTH stimulation with a two to threefold increase in both plasma cortisol and 17-hydroxyprogesterone concentrations. When the results were adjusted for the differences in basal plasma concentrations, using analysis of covariance, there was no difference in the cortisol response between the three groups of infants. In contrast, the peak plasma 17-hydroxyprogesterone response in preterm ill infants was significantly higher than the response in term ill infants ($p<0·01$).

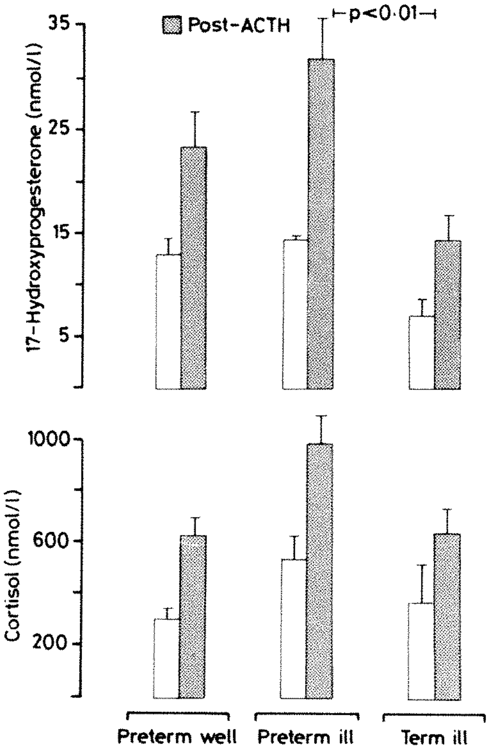

Fig. 1 *Plasma concentrations of 17-hydroxyprogesterone (upper panel) and cortisol (lower panel) before and after ACTH stimulation in newborn infants. Values are mean (SEM).*

Conversion: SI to traditional units—17-hydroxyprogesterone: 1 nmol/l≈0·31 ng/ml. Cortisol: 1 nmol/l≈0·036 μg/100 ml.

Table 1 *Clinical details of infants studied*

Group (n=)	*Birth weight (g)*		*Gestation (weeks)*	
	Mean (SD)	*Range*	*Mean (SD)*	*Range*
Preterm well (15)	1660 (462)	0·87–2·4	32·8 (2·6)	28–36
Preterm ill (26)	1568 (542)	0·82–2·7	31·4 (2·8)	28–35
Term ill (11)	3080 (533)	2·57–4.49	38·9 (1·04)	38–41

Table 2 *Mean (SEM) plasma cortisol and 17-hydroxyprogesterone response to ACTH stimulation*

Group	*Cortisol (nmol/l)*		*17-hydroxyprogesterone (nmol/l)*	
	Basal	*Peak*	*Basal*	*Peak*
Preterm well	306·3 (44·5)	631·3 (77·5)	12·9 (2·68)	23·6 (3·45)
Preterm ill	536·9 (93·9)	996·1 (136·3)	14·7 (1·75)	32·1 (3·5)
Term ill	372·4 (156·7)	646·6 (100·5)	7·2 (1·5)	14·2 (2·9)

Conversion: SI to traditional units—Cortisol: 1 nmol/l≈0·036 μg/100 ml. 17-hydroxyprogesterone: 1 nmol/l≈0·31 ng/ml.

Basal plasma cortisol concentrations were undetectable (<28 nmol/l (<1 μg/100 ml)) in five infants (9·6% of the total). Table 3 summarises the clinical details of these infants and the individual plasma cortisol responses to ACTH stimulation. The plasma cortisol concentration increased into the normal range in each infant after acute ACTH stimulation.

Table [illegible] *Plasma cortisol response to ACTH stimulation with undetectable basal cortisol concentrations*

Clinical condition	*Birth weight (g)*	*Gestation (weeks)*	*Cortisol (nmol/l)*	
			Basal	*Peak*
Hypoplastic left heart syndrome	2750	39	<28	704
Birth asphyxia	3800	41	<28	378
Diaphragmatic hernia: neonatal surgery	3250	39	<28	204
IRDS: ventilated	2360	33	<28	285
IRDS: intraventricular haemorrhage	820	31	<28	373

Conversion: SI to traditional units—Cortisol: 1 nmol/l≈0·036 µg/100 ml.
IRDS=idiopathic respiratory distress syndrome.

Discussion

Simultaneous measurements of plasma cortisol and 17-hydroxyprogesterone concentrations in newborns before and after acute ACTH stimulation have not been reported previously. The use of sensitive and specific radioimmunoassays for both cortisol and 17-hydroxyprogesterone concentrations permitted measurement of these steroid concentrations in routine capillary heel prick samples collected from small infants.

Basal plasma cortisol and 17-hydroxyprogesterone concentrations were higher in preterm infants compared with term ill infants. In the case of 17-hydroxyprogesterone, concentrations in preterm ill infants were significantly higher. This confirms results obtained in a previous study[4] and emphasises the need to determine normal values for plasma steroid concentrations in relation to gestational age. In pilot newborn screening programmes for congenital adrenal hyperplasia,[14–16] there have been unacceptably high false positive rates from raised blood spot 17-hydroxyprogesterone concentrations in ill preterm infants with non-adrenal disorders.

It is standard practice to give a synthetic 1–24 amino acid residue of natural ACTH as a short term test of adrenal insufficiency. The usual dose, 250 µg given either intramuscularly or intravenously, is probably far in excess of that required to produce maximum steroidogenesis in adults,[17] let alone preterm infants. In a recent study of the 17-hydroxyprogesterone and cortisol responses to different doses of exogenous ACTH compared with those obtained using insulin induced hypoglycaemia as a 'physiological' stimulus, it was shown that the appropriate ACTH dose infused over 10 minutes was 0·2 µg/kg.[18] This produced a response indistinguishable from the plasma cortisol response to hypoglycaemia. For our study, a Synacthen dose related to body weight was chosen based on previous experience with ACTH stimulation tests in children.[19] All three groups of infants responded with an appropriate increase in plasma cortisol and 17-hydroxyprogesterone concentrations. Previous studies, using plasma cortisol determinations only, have also shown substantial neonatal adrenocortical responses to ACTH even after prenatal administration of dexamethasone.[5 10] This is the first reported study of the use of plasma 17-hydroxyprogesterone measurements as an index of ACTH responsiveness in newborn infants. The data for this age group complement the nomograms developed by New *et al*[20] in older children relating basal and ACTH stimulated concentrations of 17-hydroxyprogesterone to distinguish different forms of 21-hydroxylase deficiency.

Roughly 10% of infants in this study had basal plasma cortisol concentrations that were undetectable. An early gestational age was not a factor, but all five infants were very ill. There was an adequate rise in cortisol concentrations after acute ACTH stimulation. The reason for this transient adrenal insufficiency is not clear. There is a pronounced change in the pattern of adrenal steroidogenesis during early adaptation to extrauterine life.[21] The concentration of placental steroids such as progesterone and oestradiol are cleared rapidly from the neonatal circulation. This removes the inhibiting effect on adrenal 3βol-hydroxysteroid dehydrogenase activity, which is essential for the synthesis of Δ^4-3-hydroxysteroids such as cortisol and aldosterone. Fetal adrenal cells maintained in tissue culture secrete predominantly Δ^5-3β-hydroxysteroids, but are exquisitively sensitive to ACTH and change to a pattern of Δ^4-3-hydroxysteroid secretion.[22 23] Perhaps this switch in enzyme activity was mediated in vivo after exogenous ACTH stimulation in those infants with low basal plasma cortisol concentrations. ACTH also serves to induce a transcriptional increase in synthesis of new enzyme and hence maximal steroidogenesis. Thus, in part, the effect of exogenous ACTH may be mediated via 21-hydroxylation of 17-hydroxyprogesterone where there is partial deficiency of 21-hydroxylase activity. Figure 2 summarises diagrammatically a possible explanation for the response observed in vivo to acute ACTH stimulation in early extrauterine life. Pituitary ACTH secretion, which normally responds to stress at delivery even after prenatal treatment with dexamethasone,[24 25] is possibly deficient due to decreased production of hypothalamic corticotrophin releasing factor. Now that synthetic corticotrophin releasing factor is available for clinical use,[26] it may be possible to study hypothalamic-pituitary-adrenal function in stressed preterm and term infants in more detail.

Normal adrenal steroidogenesis is clearly essential

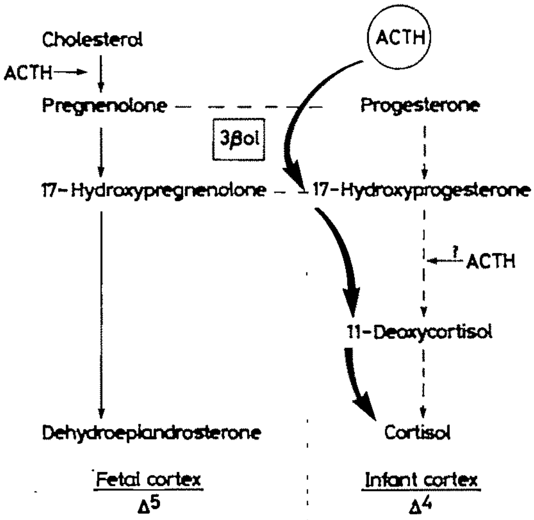

Fig. 2 *An hypothesis for the effect of exogenous ACTH stimulation on adrenal steroidogenesis in the newborn. 3βol refers to the enzyme, 3β-hydroxysteroid dehydrogenase.*

for survival after birth. With direct assays for cortisol using only 20 µl plasma now available,[13] it is possible to rapidly identify stressed infants whose basal cortisol concentrations may be abnormally low. Temporary administration of exogenous ACTH or glucocorticoid replacement may be beneficial in the management of such infants in early neonatal life.

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The nutritional cost of measles in Africa

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SUMMARY A 24 hour energy balance study was carried out on 20 black Kenyan children with acute measles and repeated after recovery. The energy content of a weighed 24 hour food intake and of a simultaneous collection of faeces and urine was determined by bomb calorimetry. Energy expenditure was measured by indirect calorimetry using a purpose built flow over calorimeter. The nutritional state of the children was assessed by anthropometry at the time of each study and during convalescence. The results showed a fall of roughly 75% in the intake of gross and metabolisable energy during measles, while the resting energy expenditure was little affected. Thus the severe degree of negative apparent energy balance observed during measles is the combined effect of underfeeding in ill children, and failure, during starvation related to infection, of the early fall in metabolic rate that characterises simple underfeeding.

Infection is commonly accompanied by a period of negative energy and nitrogen balance. This results from a reduction in dietary energy intake,[1 2] a sustained or increased level of energy expenditure,[3] and an enhanced rate of endogenous protein catabolism.[4] The development of syndromes of malnutrition after underfeeding in adults with postoperative infection has also been documented.[5] Despite circumstantial evidence of a causative link with malnutrition,[6] infection is often stated to be of secondary importance in the genesis of Third World malnutrition.[7] It was, therefore, of interest to determine experimentally the nutritional cost of a common childhood infection.

Measles was a suitable model for study; the severe illness in Africa is associated with anorexia, stomatitis,[8] and diarrhoea with loss of protein into the gut.[9] It is also followed by a period of depressed cell mediated immunity, favouring the development of opportunistic infection, including protracted diarrhoea.[10] Measles has also been implicated as a cause of malnutrition.[11 12]

The contribution to the nutritional cost of measles of changes in energy intake or expenditure may be compared by detailed study of energy balance during the acute infection. It is also possible by appropriate selection of subjects to investigate the relation between initial nutritional state and the nutritional cost of measles infection. A 24 hour energy balance study was carried out on 20 black Kenyan children during their admission with measles to the Infectious Diseases Hospital, Nairobi. The children were readmitted for the control study after convalescence, the course of which was monitored during regular home visits.

Subjects and clinical management

Table 1 summarises the clinical features of measles in the 20 children studied. Diagnosis was based in

Table 1 *Prevalence and duration of the major clinical features of measles in the 20 children studied*

Stage of the infection	*Clinical feature*	*Prevalence (%)*	*Duration in days*	
			Average	*Range*
Prodromal period	Fever	100	6	3–14
	Anorexia	100	6	3–30
	Diarrhoea	70	5	1–7
	Cough	20	6	3–10
Exanthem (hospital admission)	Rash	100	4	3–5
	Conjunctivitis	80	*	*
	Stomatitis	95	*	*
	(palatal involvement)	30	*	*
	Otitis media	35	*	*
	Laryngitis	40	*	*
	Bronchopneumonia	30	*	*
Convalescence	Anorexia	65	19	10–40
	'Loss' of walking	60	19	10–40
	Otitis media	20	*	*
	Diarrhoea	45	*	*
	Bronchopneumonia	10	5	4–7

*Not quantified.

Table 2 *Nutritional state of the 20 children at time of admission with acute measles and net changes in several nutritional variables during convalescence*

Case no	*Age (months)*	*Interstudy interval (days)*	*Initial weight (kg)*	*Net weight change (kg)*	*Actual/expected weight change (%)*	*Initial weight/length (SD score)*	*Net change in weight/length (SD score)*	*Net change in length/age (SD score)*
1*	78	22	19·0	0·50	352	−1·4	+0·3	−0·1
2	15	31	10·8	1·15	535†	+0·6	+0·4	−0·5
3	13	44	8·5	0·09	26	−1·1	+0·1	−0·1
4	13	25	8·9	0·16	82	−0·9	+0·1	−0·4
5	42	44	9·6	1·98	784†	−3·6‡	+2·0	−0·2
6	17	28	9·0	0·80	447†	−1·8	+0·1	+0·1
7	60	28	14·1	2·43	1578†	−2·1‡	+2·1	−0·4
8	18	26	12·5	1·56	945†	+0·1	+0·4	−0·2
9	52	185	11·9	1·22	120	−2·5‡	+0·5	−0·5
10	24	16	11·5	1·29	1307†	−0·7	+0·2	−0·3
11	15	76	6·7	1·17	227	−2·7‡	+1·6	−0·6
12	14	76	7·1	0·67	124	−2·7‡	+1·2	−0·9
13	22	57	10·7	1·73	491†	−1·6	+1·6	−2·0
14	41	57	14·3	2·02	622†	−1·5	+1·9	−0·9
15	46	83	13·0	1·38	299	−1·3	+1·3	−0·1
16	19	57	10·3	0·20	57	−1·2	+0·1	−0·1
17	29	64	11·0	1·96	527†	−1·0	+0·5	−0·2
18	14	44	7·7	0·65	207	−2·3‡	+1·1	−0·4
19	14	70	6·0	0·12	24	−2·6‡	−0·2	−0·2
20	16	51	8·9	0·86	259	−2·5‡	+1·1	−0·8
Mean	28·1	54·2	10·57			−1·6	+0·87§	−0·44‖
SE	4·2	8·2	0·68			0·25	0·167	0·103

*Only female subject.
†'Rapid' weight gain; rate in excess of 400% of reference weight gain.
‡Malnutrition indicated by deficit >2·0 SD from weight/length reference median.
§Significant p<0·01 improvement in mean SD score for weight/length.
‖Significant p<0·01 deterioration in mean SD score for length/age.

each case on the presence of an unequivocal rash, which was maculopapular in 13 children and black and haemorrhagic in seven. Ten children entered the study within 24 hours of the occurrence of the measles rash, and all were studied within five days of its eruption. Routine medical care was maintained during the 24 hour observation period, including administration of standard antibiotic prophylaxis. The standard hospital 'toddler diet', which is based on traditional Kenyan foods, was supplied during both clinical studies. Interference with the customary parental supervision of the children's food intake was limited to the essential cooperation involved in collecting the duplicate diet.

Table 2 illustrates the nutritional state of the children at entry to the study. Eight children were identified as malnourished on the basis of a deficit of more than 2 SD from the weight/length reference median.[13 14 15]

Experimental methods

Energy expenditure was measured by indirect calorimetry, using a purpose built system (Figure) capable of measuring both the oxygen and carbon dioxide components of the respiratory gaseous exchange. The accuracy of the assembled calorimetry, whose calibration is described elsewhere,[15] was shown in oxygen recovery tests to be mean (SD) 103 (3·5%). The metabolic rate was calculated from the respiratory gaseous exchange and the urinary nitrogen excretion.[16]

Between one and five measurements of metabolic rates were made during sleep or quiet rest, each of at least 20 minutes' duration, during the 24 hour observation period. Measurements made up to and including four hours after a meal of at least 25 kJ were arbitrarily defined as 'post prandial', while those made after a longer period were defined as measurements of 'resting metabolism'. The number of measurements made on each subject was dependent both on the child's compliance and on mains electricity. Bias due to unequal numbers of observations was eliminated by calculating a mean value for each subject of all measurements of metabolic rate and for respiratory quotient made during either resting or post prandial metabolism (Table 3).

The dietary intake of gross energy was measured by collecting a 24 hour duplicate diet, homogenising it, drying an aliquot and determining its heat of combustion by bomb calorimetry. Faeces and urine were collected over the same period using urine collecting bags and lined disposable napkins as indicated. Faecal material was extracted from the napkins,[17] dried, and then analysed by bomb calor-

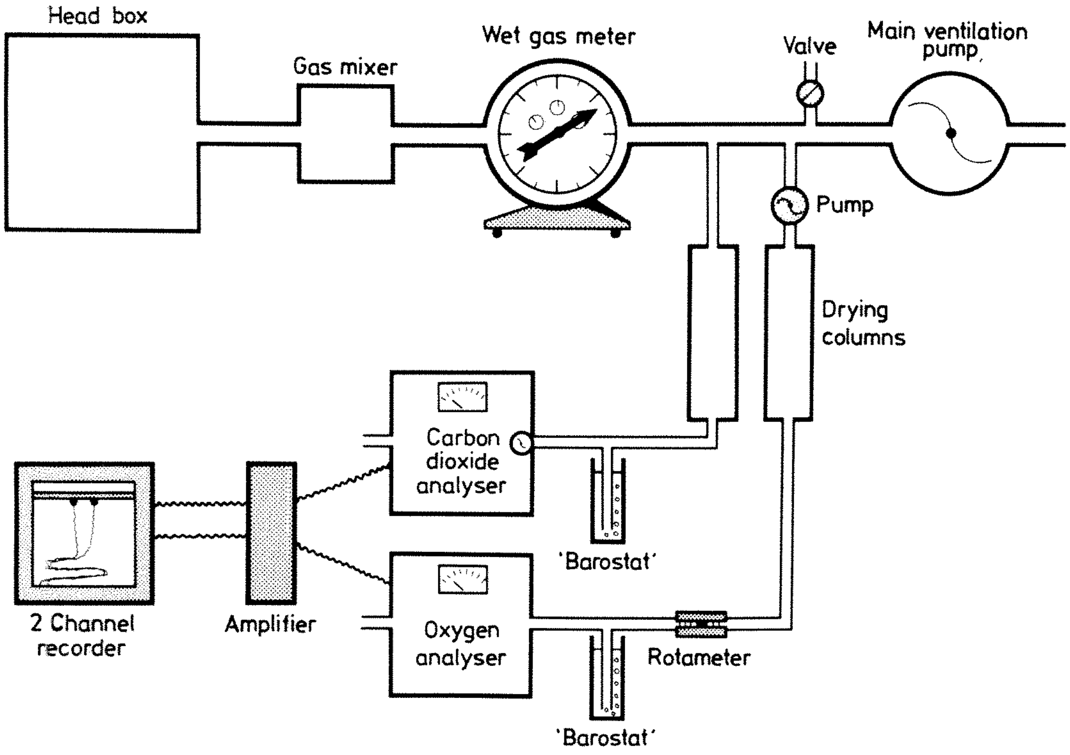

Figure *The flow over calorimeter: circuit diagram.*

Table 3 *Energy expenditure (metabolic rate) in 20 children studied during and after acute measles and in relation to food intake. Values are mean (SE)*

Variable measured	*Infection (children studied during measles)*		*Control (children studied after measles)*	
	Resting	*Post prandial*	*Resting*	*Post prandial*
Oxygen consumption (ml/kg/min)	8·8 (0·34)	8·2 (0·67)	9·3 (0·32)	10·3 (0·46)
Metabolic rate (kJ/kg)	10·7 (0·39)	9·7 (0·61)	11·3 (0·36)	12·8 (0·58)
Respiratory quotient	0·83 (0·02)	0·80 (0·03)	0·98 (0·03)	0·93 (0·02)
No of subjects*	18	8	18	16
Total no of observations	30	19	31	28

*No of subjects (mean values of all observations) studied at the stated period. Statistical analysis by Student's t test. Mean level of resting metabolic rate and resting oxygen consumption similar in both studies. $p<0{\cdot}05$ (Paired data) for post prandial *v* resting metabolic rates in control; $p<0{\cdot}05$ (paired data) for post prandial metabolic rate in control *v* post prandial metabolic rate in infection; $p<0{\cdot}05$ (unpaired data) for post prandial *v* resting oxygen consumptions in control; $p<0{\cdot}01$ (unpaired data) for post prandial oxygen consumption in control *v* post prandial oxygen consumption in infection. Mean level of resting respiratory quotient significantly higher in control than infection, $p<0{\cdot}01$ (paired data).

imetry. Food and faeces were analysed in duplicate with a third analysis when results failed to agree within 3%. The energy content of urine was calculated from its urinary nitrogen content, which was determined by a modified Kjeldahl method. Bomb calorimetry was carried out in the Wellcome Trust Research Laboratories, Nairobi, and urinary nitrogen analyses in the Department of Surgery Laboratories, Northern General Hospital Sheffield, by Mr A Prescott. Urine was stored at −20°C and transported frozen for analysis. Results of these analyses were then used to calculate the 24 hour intake of gross, digestible, and metabolisable energy.

Full auxological measurements were made at the beginning of each 24 hour clinical study, and children were weighed at each home visit. Weight and length measurements using a basket type beam balance (CMS, London) accurate to 10 g and an infant measuring table (Holtain) accurate to 0·1 cm were used to calculate the weight:length ratio. This was referred to the reference standard recommended by the World Health Organisation[14] using the standard deviation score method of presenting data to facilitate parametric statistical analysis.[18] The weight measurements were also used to calculate the net rate of weight gain during convalescence, which was expressed as a percentage of the reference rate adjusted for age. Informed verbal consent was obtained from all parents, and the study was considered acceptable by the Medical Research Ethical Committee of Kenyatta National Hospital.

Results

The magnitude and pattern of energy expenditure. In children studied with acute measles the mean level of the metabolic rate was similar during both post prandial and resting metabolism, with no evidence of the significant ($p<0{\cdot}05$) post prandial enhancement of metabolic rate that was observed in the control study (Table 3). Thus the level of the resting metabolic rate was similar in both studies, while the mean post prandial metabolic rate was significantly higher in the control study ($p<0{\cdot}05$), the difference representing 24% of the mean value of the post prandial metabolic rate in control patients. Paucity of data on the post prandial metabolic rate during infection precluded analysis of the relation between the magnitude of this rate and initial nutritional state.

The mean level of the respiratory quotient during both resting and post prandial metabolism was significantly different in infection and control studies ($p<0{\cdot}001$). The significant increase in the mean respiratory quotient of recovered children was true both for well nourished and previously malnourished children ($p<0{\cdot}01$ in each case). The mean level of the respiratory quotient in the control study was, however, higher in those children who had initially been malnourished ($p<0{\cdot}05$), although this was not attributable to rapid rates of weight gain during convalescence.

The intake of gross, digestible, and metabolic energy. The mean level of intake of gross energy was significantly reduced during measles ($p<0{\cdot}001$), this reduction, when expressed in kJ/kg/24 h, representing a 75% fall in the energy intake. The mean level of gross energy intake was not significantly influenced in either study by the initial nutritional state. While the faecal energy loss was, in absolute terms, greater in the control study, the digestible energy represented a similar percentage of gross energy in each study (Wilcoxon's rank sum test). Conversely, although the urinary energy loss was of similar magnitude in both studies, the consequent percentage reduction in energy intake was greater during infection ($p<0{\cdot}05$, Wilcoxon's ranked sum test for paired data) (Table 4). Thus the percentage of gross energy intake that was metabolisable was significantly smaller during acute measles than after recovery ($p<0{\cdot}05$, Wilcoxon's ranked sum test).

Apparent energy balance. As a result of the fall in metabolisable energy intake and a sustained level of energy expenditure during measles, 17 of the 18 children on whom data were complete were in negative apparent energy balance at the end of the 24 hour study. Conversely, 12 of 18 children were in positive apparent energy balance during the control study. The magnitude of the mean negative energy balance during measles is given by −169 (21·7) kJ/kg/24 h and of positive balance after recovery by 67 (30·0) kJ/kg/24 h.

Convalescence. As illustrated in Table 2 the mean level of nutrition as estimated by the weight/length SD score had significantly improved by the time of the control study ($p<0{\cdot}01$). Nevertheless, this was

Table 4 *Energy intake and resting energy expenditure by 20 children during and after measles; illustrating proportions of gross energy digestible and metabolisable after energy loss in faeces and urine, respectively. Values are mean (SE)*

	Infection			*Control*		
	kJ/24 h	*%*	*kJ/kg/24 h*	*kJ/24 h*	*%*	*kJ/kg/24 h*
Gross energy intake	897 (126·0)	100	94·1 (18·5)*	4288 (457·2)	100	374·2 (29·6)
Faecal energy loss	95 (28·8)		6·5 (1·5)	437 (75·4)		36·7 (7·2)
Digestible energy intake	825 (121·2)	92†	90·3 (17·6)	3895 (416·6)	87	322·1 (33·3)
Urinary energy loss	104 (12·9)		10·9 (1·3)	175 (32·4)		12·8 (1·9)
Metabolisable energy intake	742 (123·6)	72‡	81·5 (17·5)	3731 (489·4)	83	309·4 (32·8)
Resting energy expenditure	2574 (183·2)		256·6 (9·34)	3180 (226·2)	272·2 (8·66)	

*Gross energy intake significantly reduced during measles, $p<0{\cdot}001$ (Student's *t* test for paired data).
†Digestible energy equivalent to similar percentage of gross energy intake in both studies (Wilcoxon's paired rank sum test).
‡Metabolisable energy intake equivalent to significantly lower percentage of gross energy intake during measles, $p<0{\cdot}05$ (Wilcoxon's paired rank sum test).

accompanied by a significant deterioration in the mean length/age SD score ($p<0\cdot01$). Neither initial nutritional state nor the presence of complicating pneumonia was associated with a lower rate of weight gain. Children with rapid rates of weight gain, however, had a significantly lower prevalence of diarrhoea during convalescence ($p<0\cdot01$, χ^2 analysis). In summary, measles infection was characterised by a 75% fall in gross and metabolisable energy intake. Energy expenditure remained at control levels, although the post prandial enhancement of the metabolic rate was absent during infection. The satisfactory mean rate of weight gain during convalescence did not seem to be influenced by the initial nutritional state nor the severity of the clinical infection, although it was significantly inhibited by late onset diarrhoea.

Discussion

These data show that the normal pattern of positive energy balance in childhood may be reversed by measles infection. The major factor responsible was the grave reduction in the intake of gross dietary energy. Although this has been quantified only for a 24 hour period, the universal parental reporting of previous anorexia (Table 1) suggests that negative energy balance was of a longer duration.

The development of overt malnutrition after infections complicated by anorexia and often by starvation treatment is not merely an effect of underfeeding.[2] [19] Starvation associated with infection results in a more rapid and severe weight loss than does starvation alone.[20] This seems to be due to an increase in resting metabolic expenditure during infection stress[5] [21] rather than the early fall in metabolic rate that characterises starvation or underfeeding.[22] [23] The present data, while not immediately showing an increase in resting metabolic rate during measles, afford no evidence of any metabolic adaptation to starvation. However, review of the respiratory quotient data on the control group, 67% of whom were in positive apparent energy balance, eating a high carbohydrate diet, suggests a further interpretation. The high mean value of the resting respiratory quotient, and the fact that the value for respiratory quotient exceeded 1·0 in 20 out of 31—that is, in 65% of all observations of resting respiratory quotient—was strongly indicative of net lipogenesis from carbohydrate. The persistence of lipogenesis—that is, biosynthesis—long after the post prandial period suggested that the resting metabolic rate included the energy cost of this biosynthesis. As net biosynthesis was manifestly absent in the infection study, the sustained level of the resting metabolic rate at this time was probably indicative of an increased basal metabolic rate. Thus the basal metabolic rate seems to be increased in children with measles as it is with other viral infections.[24]

No attempt was made to interpret weight changes during the acute febrile illness, as they were probably influenced by alteration in fluid as well as energy balance at this time.

Although there was a high prevalence of secondary infection during convalescence (Table 1), only in the case of diarrhoea was a significant effect observed. An even higher prevalence of diarrhoea after measles with graver nutritional sequelae has been reported in a rural population with less easy access to mains water.[9] The overall improvement in nutritional state, estimated by the mean weight/length SD score, seemed to be the combined effect of an increase in weight and sluggish or absent linear growth. A link between measles and nutritional stunting has also been reported in Nigerian children.[25]

Malnutrition did not seem to influence the magnitude of negative energy balance observed in the present study. However, catabolic weight loss to meet a given energy shortfall would probably be greater in an already lean child because of quantitative differences in the energy stored in lean and fatty tissue. This supposition accords with the observation of a more severe weight loss in postsurgical sepsis in lean adults.[21]

The return of all 20 children for control study was the result of regular surveillance, accompanied by medical intervention, during the period of convalescence. Nevertheless, four children failed to achieve reference rates of weight gain, and one child, whose recovery was interrupted by malaria and pneumonia, had become severely wasted by the time of the second study.

The nutritional cost of measles has been quantified by means of a 24 hour energy balance study. The resultant negative apparent energy balance is the combined effect of a grave reduction in the intake of gross and metabolisable energy and a sustained level of resting metabolic expenditure. Stopping of growth during infection is shown by absence of the usual post prandial increase in metabolic rate and suggested by the pronounced fall in the level of respiratory quotient during acute measles. Despite a period of negative energy balance most children gained weight satisfactorily during convalescence, although linear growth had slowed. Four children, only one of whom was previously malnourished, failed to thrive throughout follow up. The experimental results of this study support previous circumstantial evidence that measles, and, by inference, other infections associated with negative energy balance, are probably implicated in the genesis of childhood malnutrition.

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Dietary survey of diabetics

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SUMMARY This study of 168 diabetic children from Tyneside and Teesside aimed to record what the children actually ate and to compare this with both their prescribed diet and current recommendations. The amounts of energy consumed were similar to those expected of non-diabetic children, but the components of the diabetic children's diets were different, consisting of more fat and fibre, but less sugars and carbohydrates. They ate more carbohydrate than prescribed but less than current recommendations as there was a shortfall between the amount prescribed and that suggested in the recommendations. Diabetic control was related to the amount of fibre consumed and to compliance with the prescribed diet, but not to the proportion of energy taken as carbohydrate. The insulin dose was slightly lower in those children eating more fibre.

The modification of diet has been a cornerstone of the treatment of diabetes mellitus for many years, although a great variety of prescriptions have been used.[1] Typically, dietary treatment restricted carbohydrate to approximately 40% of the energy intake and limited added sucrose. Compliance with and benefits from such regimens have been claimed to be poor.[2,3]

It has recently been suggested that this policy leads to an increased fat intake which may contribute to the diabetic's liability to vascular complications.[4] Furthermore, benefits from eating increased amounts of fibre have been reported[5] and disputed.[6] This information led to revised recommendations for the diets of diabetics.[4] Briefly, these recommendations suggest that energy intake is of prime importance, but that only 35% of the energy should be provided by fat, which implies a carbohydrate intake of at least 50%. Most of this carbohydrate should be consumed as polysaccharides rich in fibre. It is still considered important to exclude rapidly absorbed mono- and disaccharides. These recommendations are similar to those suggested for the general population.[7]

The aim of this study was to investigate the relations between intake, recommendations, and prescribed diet in children with diabetes.

Methods

Between July 1983 and March 1984 children attending the diabetic clinics at the Royal Victoria Infirmary and the General Hospital, Newcastle upon Tyne; the Queen Elizabeth Hospital, Gateshead; North Tees General Hospital; and Middlesbrough General Hospital were invited to take part in a detailed audit. The study was described in detail to the parents (and children) both orally and in a letter. Ethical approval for the study was obtained from the appropriate local committees.

As part of this audit, current practice was assessed by means of a diary kept by the parents or child, or both, for three consecutive days. In it they were asked to record all dietary intake and the insulin regimen. The amount of food consumed was estimated in household measures and the time of consumption was also recorded. This information was then converted at an interview (lasting approximately 30 minutes) on the fourth day to estimates of the weight of each item consumed. Computerised food tables[8] were subsequently used to calculate the intake of nutrients. This procedure has been used previously and is described more fully elsewhere.[9]

At a special clinic a structured questionnaire was used to obtain social information, and the child was examined physically. The parent or child completed a test of practical skills and a multiple choice questionnaire to assess knowledge of diabetes. A blood sample was also requested for estimation of glycosylated haemoglobin AI (HbAI) and random C peptide.

Intakes were compared with recommendations for groups of children,[10] and the amount of carbohydrate recommended for diabetics was calculated as

50% of this recommended energy intake[2] as appropriate for age and sex. Compliance with the dietary prescription was calculated by subtracting the weight of carbohydrate prescribed from that consumed.

The data were analysed using the statistical package for the social sciences. Pearson's r correlation coefficients were calculated to test for relations between variables. Partial correlation coefficients were calculated in order to control for the effect of any variables that might have confounded the relation between dependent and independent variables.

Results

A total of 234 children were attending the clinics at the time of the study. Seven children taking part in another study and two who had severe psychological problems were not, however, invited to take part. One hundred and seventy (75·5% of those invited) completed the study. Useful dietary records were obtained from 98 boys and 70 girls, and further discussion is limited to these children.

Seventy (42%) families were classified into socioeconomic group 1, (professional and managerial), 68 (40%) into group 2 (clerical and craftsmen), 19 (12%) into group 3 (semi- and unskilled labourers), and 11 (6%) into group 4 (either unknown, unclassified, or retired). Their age distribution is shown in Table 1 together with some other clinical details. Subsequent analysis by age was made to correspond with the age groups given in the tables of 'Recommended amounts of food energy and nutrients for groups of people in the United Kingdom'.[10]

The intakes of energy and carbohydrate are summarised in Table 2 together with the recommended and prescribed daily amounts of carbohydrate. The mean energy intakes were within 10% of those recommended. The mean carbohydrate intakes, however, were consistently below those recommended (averaging 84%), only 25 children (15%) consuming more. The mean amount of carbohydrate prescribed was only 71% of the recommended level. Carbohydrate intake therefore averaged 120% of that prescribed, and only 16 (9·5%) children ate less than this. Table 2 also shows the intake of sugars and fibre and the composition of the energy intake related to age and sex. For comparison Table 2 includes results from a recent local dietary survey of non-diabetic children in which an identical survey procedure was used.[9 11] The relatively low contribution of carbohydrate to the energy intake of the diabetic children can be seen. Only eight children consumed 50% or more of their energy in this form. Total sugars contributed less to the energy intake than in the Northumberland study,[9] but fat contributed slightly more. Total sugars constituted a lower proportion of the carbohydrate intake. Furthermore, the lactose intake of the diabetic children (mean 19·2 g boys, 18·7 g girls) contributed 25% of the sugars consumed, compared with 13% in the previous study (17·1 g boys, 13·4 g girls). The fibre intakes of the diabetic children were also higher.

The Figure shows the energy intakes of the boys and girls related to their ages. Superimposed on this are the predicted energy intakes for non-diabetic children.[12] The intake of the diabetic girls seems to match the predictions closely while the boys' intake tends to be slightly below the predicted value.

The relation between the single HbAl measurement and mean dietary intake is summarised in Table 3. As HbAl was correlated to C peptide ($r=-0·319$, $P<0·01$), this was controlled for in these calculations. The age of the child was related to the intake of several nutrients (energy $r=0·610$, $P<0·01$; carbohydrate $r=0·575$, $P<0·01$; % carbohydrate $r=-0·079$, $P>0·05$; sugars $r=0·240$, $P<0·01$; % sugars $r=-0·242$, $P<0·01$; and fibre (g/MJ) $r=-0·226$, $P<0·01$), and was also used as a

Table 1 *Age distribution of those subjects who completed the dietary survey together with their mean (SD) duration of diabetes, insulin dose, weight and glycosylated haemoglobin (HbAl)*

	Age group						
	<5	*5–7*	*7–9*	*9–11*	*11–13*	*13–15*	*15+*
Sex							
Boys	9	11	11	17	26	16	8
Girls	2	5	7	12	18	19	7
Duration of diabetes (yrs)	2·0 (0·7)	1·8 (1·1)	2·9 (1·9)	3·8 (2·1)	4·3 (2·9)	5·5 (3·1)	4·7 (4·0)
Insulin dose (U/kg)	0·78 (0·12)	0·84 (0·20)	0·88 (0·19)	0·84 (0·25)	0·89 (0·29)	1·00 (0·32)	0·88 (0·31)
Weight (kg)	18·6 (1·4)	23·4 (2·7)	26·9 (3·5)	34·6 (4·9)	41·7 (6·6)	47·1 (7·3)	58·3 (5·7)
HbAl (%)	10·1 (1·7)	10·0 (1·7)	9·5 (2·2)	10·7 (2·4)	10·3 (2·1)	12·1 (1·9)	10·2 (3·4)

Table 2 *Mean daily intake of energy and proportion of energy from fat, carbohydrate (CHO) and sugars. The mean daily carbohydrate intake compared with the amount of carbohydrate prescribed and recommended are also shown. The intake of sugars as a proportion of the carbohydrate and fibre in relation to the energy intake and for comparison comparable figures from a recent local survey*[9–11] *are included*

	No	*Energy*	*CHO (g)*			*Proportion of energy (%)*			*Sugars/ CHO (%)*	*Fibre per MJ (g/MJ)*
		(MJ)	*Intake*	*Recommended*	*Prescribed*	*Fat*	*CHO*	*Sugars*		
Age group 2·5–9 yrs										
Boys	31	6·9 (1·5)	183 (35·2)	224 (21·9)	159 (29·4)	42 (4·7)	43 (4·3)	15 (4·8)	35 (8·9)	2·8 (1·0)
Girls	14	7·0 (1·3)	182 (27·1)	222 (24·6)	158 (23·8)	44 (4·5)	42 (4·4)	16 (3·4)	39 (6·8)	2·6 (0·9)
9–12 yrs										
Boys	31	8·9 (1·2)	238 (34·5)	291 (15·3)	202 (19·3)	43 (4·5)	43 (4·2)	13 (3·7)	31 (6·8)	2·6 (0·7)
Girls	19	8·8 (1·2)	238 (38·0)	257 (7·5)	192 (19·7)	43 (4·5)	43 (4·2)	16 (4·4)	36 (2·3)	2·3 (0·5)
12–17 yrs										
Boys	36	10·1 (1·8)	263 (55·7)	330 (23·9)	214 (28·8)	44 (4·1)	42 (4·1)	13 (3·3)	30 (7·0)	2·2 (0·6)
Girls	37	9·0 (1·5)	240 (42·4)	270 (0·0)	199 (27·9)	43 (3·9)	43 (4·5)	14 (4·1)	33 (7·5)	2·2 (0·6)
Northumberland study										
11·5–14 yrs										
Boys	193	9·5 (1·5)	289 (47·6)	—	—	40 (3·0)	49 (3·2)	21 (3·6)	43 (6·0)	1·5 (0·3)
Girls	212	8·5 (1·4)	256 (48·5)	—	—	40 (2·8)	48 (3·3)	21 (4·0)	44 (6·7)	1·6 (0·3)

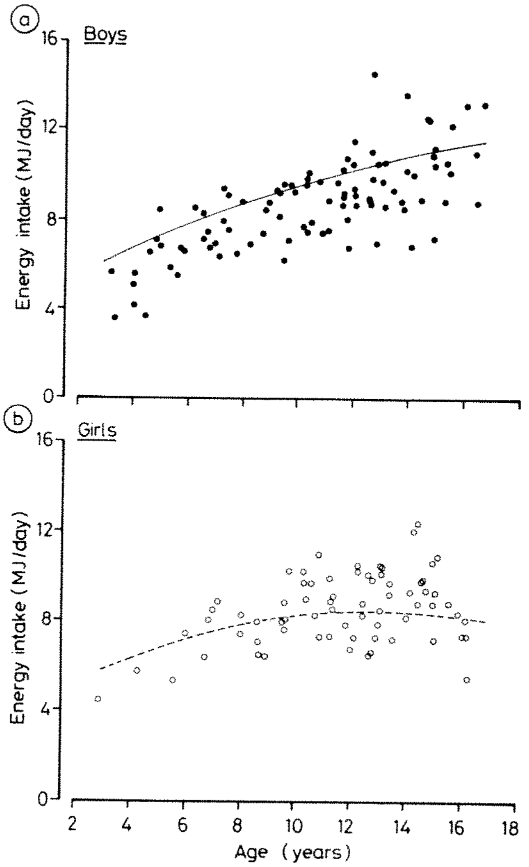

Figure *Energy intake of diabetic boys and girls related to the predicted energy intakes for non-diabetic children.*

Table 3 *Partial correlation coefficients between dietary variables and glycosylated haemoglobin (HbAl) controlled for C peptide and age**

Variables	*Second order*
Dependent	HbAl
controlling	C peptide+age
Independent	
Energy (kJ)	+0·163*
Sugars (g)	−0·001
CHO (g)	+0·118
Sugars (%)	−0·125
CHO (%)	−0·089
Sugars (% CHO)	−0·107
Fibre (g/MJ)	−0·169*
Fibre (g)	−0·031
Compliance†	+0·164*

*Only 150 subjects had successful estimations of their HbAl, C peptide and diet made.
†CHO intake minus CHO prescribed, ie the greater the discrepancy between CHO prescribed and CHO consumed the higher was the HbAl.

controlling variable. Energy, fibre (in relation to energy) and compliance with prescriptions for carbohydrate were the only factors found to relate to HbAl. The data were analysed for boys and girls separately and gave similar results.

There was an inverse relation between insulin dose and the intake of fibre (g) after controlling for C peptide and age ($r=-0\cdot182$, $P<0\cdot05$). The equivalent value for fibre per unit of energy (g/mJ) was $r=-0\cdot156$, $P=0\cdot058$. Insulin dose was not related to the other dietary variables.

There was a weak relation between duration of diabetes and % energy consumed as carbohydrate ($r=+0\cdot126$, $P=0\cdot05$) and prescription of carbohydrate ($r=-0\cdot123$, $P=0\cdot06$), suggesting that the patients who had developed diabetes recently were prescribed a more appropriate diet but actually ate less carbohydrate.

Discussion

This study has shown that there is still a tendency to prescribe amounts of carbohydrate well below those suggested in current recommendations. It was conducted at five clinics at which nine consultants and five dietitians were working, and hence no consistent dietary policy was observed. All clinics supported, in principle, the current dietary recommendations, but the slight negative relation between duration of diabetes and carbohydrate prescribed suggests that the recommendations were being applied to newly diagnosed patients more than to those with long standing disease. Some still used the 'rule of thumb' method of calculating the carbohydrate allowance—100 g plus 10 g for each year of life. The energy intakes of these diabetic children were broadly in line with those predicted for non-diabetic children, a finding similar to that of Kinmonth and Baum.[13] Therefore, in order to comply with their allowance the diabetic children were forced to complete their energy balance by consuming extra fat, and, to a smaller extent, protein. Even so their intakes of carbohydrate were above the prescribed amounts, although this was partly due to the methodology employed, which counted the carbohydrate in all foods and drinks even those usually considered to be carbohydrate free, for example cabbage and tomatoes. Widdowson, in her pre-war study of 13 diabetic children aged 5 to 17 years, concluded that their diets were lower in energy and carbohydrate but higher in fat and protein than the diets of non-diabetic children.[14] She suggested that the lower energy intakes were the result of the diabetic children leading more 'sheltered' and hence less active lives, which is now actively discouraged.

Although the children generally consumed more carbohydrate than prescribed, they consumed less than might have been expected for non-diabetic children. This is evidence of the effort made to comply with dietary instructions. Compliance, as defined here, was also found to be related to control. Account should also be taken, however, of what the child might have eaten had it not been for the dietary instructions. Although this cannot be known with certainty for our patients, it seems likely that apart from the differences in fat and carbohydrate intake, these children would have eaten more sugars (not lactose) but less fibre. Sucrose was used very little, whereas saccharine, proprietary diabetic foods, and modified recipes were much in evidence, indicating compliance despite the difficulties associated with dietary modifications.

The low prescriptions of carbohydrate may have been due to failure to review the diet often enough. Calculations show that the 'rule of thumb' method of calculating carbohydrate allowance underestimates recommended intakes for groups of subjects, especially for boys, and the margin increases with age. Carbohydrate allowances at approximately 50% of the predicted energy intake for non-diabetic children can be calculated using modifications of the regression equations of Whitehead, Paul, and Cole;[12] boys: carbohydrate $(g)=135+19\cdot0$ years$-0\cdot375$ years^2; girls: carbohydrate $(g)=119+21\cdot2$ years$-0\cdot81$ years^2. Extreme caution is advised, however, when using these methods because subjects can vary so much and there has been a tendency for the energy intake of children to fall over recent years.[12] The best method of prescribing carbohydrate is probably based on an assessment of previous energy intake. There is, however, the possibility that achieving the new recommended intakes without resort to larger intakes of refined carbohydrate is not practical. If the underprescription of carbohydrate could be successfully corrected it is likely that the intake of fibre would further increase.

The findings that the amount of fibre (g/MJ) correlated negatively with HbAl and weakly with insulin dose are in agreement with suggestions[15] that unabsorbable carbohydrate (fibre) may improve control by decreasing insulin requirements. No relation was found between the proportion of the energy consumed as carbohydrate and HbAl or insulin dose (Table 3), suggesting that the improvement in tolerance with a high carbohydrate diet[16] may be due to an increase in fibre. Caution must be urged, however, before extrapolating these results because the glycaemic response to a meal varies with the sources of carbohydrate[17] and the different fibre fractions.[18] Neither of these were identified in this study, and it is not known to what extent the lower

HbA1 values were associated with these specific dietary variables. The children in this study, however, were eating diets which were, to a large extent, self selected indicating that fibre may be a practical aid to control. Some experimental diets seem to be very unrealistic.

One experimental study has reported that the benefits of a high fibre, high carbohydrate diet may only apply to those children still producing endogenous insulin.[6] This thesis is not supported by our observations of 168 children who were continuing with their normal routines and dietary practices. There is a complex interaction, however, between parent knowledge, socioeconomic group, fibre intake, and control (unpublished observations), and so it is possible that fibre intake may only be related to HbA1 as a covariate.

Diet is commonly mentioned as the major problem encountered when looking after a diabetic child. Dietary recommendations for diabetics, however, are now similar to those for the general population.[7] This fact should be utilised when giving dietary instructions; bringing the intakes of children with diabetes more in line with the rest of the family (or vice versa) may lead to a considerable improvement in lifestyle.

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Plasma fibronectin concentrations in mucocutaneous lymph node syndrome

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SUMMARY Plasma fibronectin concentrations were measured in 41 patients suffering from mucocutaneous lymph node syndrome (MCLS, Kawasaki disease). Plasma fibronectin concentrations were decreased significantly in the early days of the disease, but increased gradually and reached significantly high concentrations by the fourth week of the disease.

In nine of the 41 patients, coronary involvement was found by echocardiographic examination. These patients showed significantly lower plasma fibronectin concentrations in the first and second weeks of the disease than those without coronary involvement.

As the underlying pathology of MCLS is known to be vasculitis, the lower plasma fibronectin concentrations might be partly the result of injury inflicted upon the endothelial cells, which are thought to be the major site of synthesis of circulating plasma fibronectin concentrations.

Fibronectin is an adhesive glycoprotein that is found on many cell surfaces and in extracellular fluids. A wide variety of its properties has been revealed recently. Plasma fibronectin is known to play a role in phagocytosis of neutrophils[1] and macrophages,[2] clearance of collagenous debris by the reticuloendothelial system,[3] wound healing, and so on.

As commercially available kits for the measurement of human plasma fibronectin concentrations are available, we have measured it in several groups of normal and diseased children.[4] Among them, patients suffering from MCLS seemed to show a distinct trend during the course of their disease.

Materials and methods

Patients. Forty one patients, who fulfilled the diagnostic criteria for MCLS prepared by the research committee of MCLS,[5] which was supported by the Ministry of Health and Welfare of the Japanese government, were included in the study. These included 21 boys and 20 girls; the ages of the patients were between 2 months and 4 years. The Table shows the patients' age and sex. Of the 41 patients, nine were shown to have some coronary involvement by echocardiographic examination, which was performed at least once in the convalescent phase, usually twice or more serially.

Table *Distribution of patients according to sex and age. (Values in parentheses are No of patients with coronary involvement)*

Age (yrs)	*No*	*Boys*	*Girls*
<1	11	7 (3)	4 (2)
1–<2	14	6 (1)	8 (1)
2–<3	7	5 (1)	2 (0)
3–<4	7	2 (1)	5 (0)
4–<5	2	1 (0)	1 (0)
Total	41	21 (6)	20 (3)

Samples. Blood samples were drawn by venipuncture from patients with MCLS. Plasma was separated with sodium citrate and stored at −40°C until assayed. A total of 165 samples were collected from the 41 patients. One to 12 samples were obtained from each patient on days ranging from days 2 to 92 of the disease.

Measurement. A commercially available kit for determination of human plasma fibronectin concentrations, issued by Boehringer Mannheim Yamanouchi Co Ltd, was used. The principle of this test is a kinetic turbidimetric measurement of the antigen-antibody reaction.

Consent. Consent for the sampling was obtained from all parents of the MCLS patients.

Statistical analysis. The groups were compared using the *t* test and Welch's test according to the sample distribution.

Results

Changes in plasma fibronectin concentrations during the days after onset are shown in Figure 1. The shaded area represents the normal range of plasma fibronectin concentrations for infants and children in our hospital.[4] The decreased plasma fibronectin concentrations in the early days of the disease and the following tendency to increase are obvious. Figure 2 represents the plasma fibronectin concentrations in patients with MCLS classified according to the day of sampling from the onset of disease. The concentration (173 (SD 58) mg/l, n=24) in the first week of the disease was significantly decreased, and the values at the fourth, sixth, and seventh week or later were significantly increased compared with the normal values in our hospital.

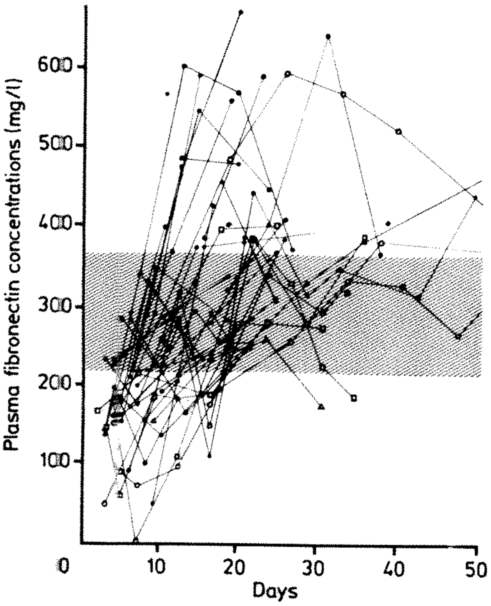

Fig. 1 *Serial measurement of plasma fibronectin concentrations in each patient with MCLS. (——●—— = without coronary involvement; ——○—— = with aneurysm; ——△—— = with dilatation; ——□—— = with irregularity of coronary artery wall in echocardiographic examination.) Shaded area represents the normal range in our hospital.*

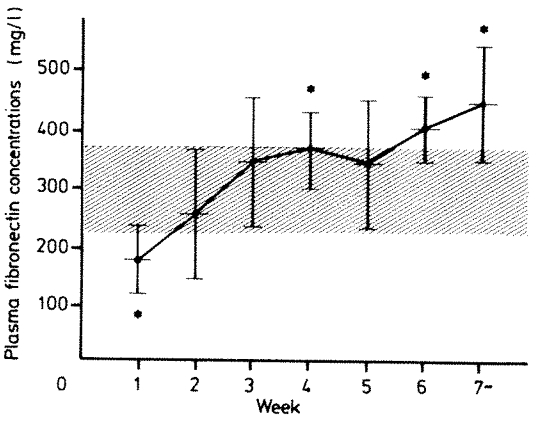

Fig. 2 *Plasma fibronectin concentrations in patients with MCLS and date of sampling. Shaded area represents the normal range in our hospital; brackets represent mean (SD).*

*p<0·01.

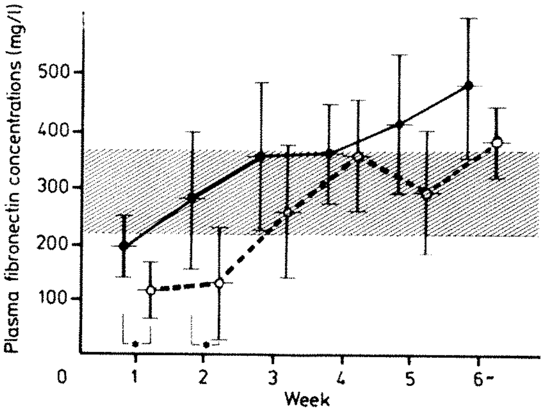

Fig. 3 *Plasma fibronectin concentrations in patients with MCLS: comparison between those with (– – ○ – –) and without (—●—) coronary involvement. Shaded area represents the normal range in our hospital; brackets represent mean (SD).*

*p<0·01.

The plasma fibronectin concentrations in patients with MCLS without coronary involvement were higher than those with coronary involvement at any week of the disease that had been measured (Fig. 3). In the first and second week of the disease, particularly, the differences between those with and without coronary involvement were significant. The number of samples included were 109 samples from 32 patients without coronary involvement and 56 samples from nine patients with coronary involvement.

Discussion

The cause of MCLS is not yet known, although some bacteria, viruses, and toxins are thought to participate in the pathogenesis of this condition. Plasma fibronectin is known to act as a non-specific opsonin for the reticuloendothelial system.[3] Accordingly, it is possible to attribute the reduced plasma fibronectin concentrations to its consumption during the clearance of macromolecules such as immune complexes or bacteria. Another reason for the decreased concentrations of plasma fibronectin in the early stage of MCLS, however, may be that, because the underlying pathology of MCLS is vasculitis,[6] there may be damage to the endothelial cells, which are thought to be a major site of synthesis of plasma fibronectin.[7] If this is indeed the case, the degree of decrease of the plasma fibronectin concentrations may reasonably correlate with the degree of vasculitis of the coronary artery as well as with the degree of coronary involvement. Plasma fibronectin concentrations are known to be lower in younger individuals,[4] in whom coronary involvement is more commonly observed, as shown in the Table. It was therefore suspected that the lower plasma fibronectin concentrations in patients with coronary involvement might be due to the age groups concerned. To investigate this possibility, the plasma fibronectin concentrations in patients with and without coronary involvement were compared with those in each age group, and the results confirmed that the concentrations were lower in patients with coronary involvement, irrespective of age (data not shown).

The treatment of MCLS is not yet established. At present, it is important to detect coronary involvement as early as possible. Nowadays, echocardiographic examinations are conveniently available at almost every hospital or clinic, and serial and meticulous follow up study using echocardiographic examination is the standard method of management of MCLS in this country. Unfortunately, coronary involvement cannot be detected with this method until it becomes obvious. It seems valuable, therefore, to anticipate coronary involvement in patients with MCLS. If a low initial fibronectin concentration is a possible indicator of subsequent formation of aneurysms the determination of plasma fibronectin concentrations in patients with MCLS will be of some clinical use in selecting more severely affected patients for aggressive treatment. In terms of the subsequent increments in plasma fibronectin concentrations in patients with MCLS, no appropriate explanation can be given at present. It might, for example, be the result of an overshoot in production in the replenishing process.

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Intussusception—current trends in management

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SUMMARY Barium enema reductions were attempted in 65 (90%) of 72 intussusceptions, of which 51 (79%) were successful. This represents a success rate of 70% overall. The average hospital stay was 3½ days. There was no mortality and, apart from a recurrence rate of 10%, no morbidity. It is suggested that barium enema reduction should be the treatment of choice provided that there is an emergency service of a paediatric radiologist and the patient is adequately resuscitated, the only absolute contraindication being evidence of pneumatosis intestinalis or peritonitis. Those patients who presented with shock, rectal bleeding, duration of symptoms longer than 48 hours, and pronounced degree of bowel obstruction had a higher rate of unsuccessful reduction. However, only the last two were significant. Further, provided that the clinical condition remains satisfactory and the reduction has been achieved to the caecum, a repeat barium enema after some hours may be successful in achieving reflux of contrast into the ileum, confirming complete reduction.

Recently, there has been a trend towards the use of barium enema reduction in the treatment of intussusception. This paper reviews and analyses all those patients treated with barium enema reduction at our hospital and looks into the factors that are in favour for or against its use.

Patients and methods

All patients with intussusception admitted into the hospital from June 1977 to December 1983 inclusive were studied. There were 66 patients with 72 cases of intussusception (six recurrences). The diagnosis was confirmed either radiologically or at operation. There were 46 boys and 20 girls. Sixty eight cases (94%) were under one year of age (mean 6·5 months). Abdominal pain and vomiting occurred in 64 (89%) cases and rectal bleeding in 36 (50%). A palpable abdominal mass was found in 53 (74%) cases and in two (3%) the mass was palpable per rectum. Blood was found at rectal examination in 47 (65%) cases. Thirty two (44%) were noted to be dehydrated on admission, and four (6%) were in shock. Plain films of the abdomen were taken in all cases and showed moderate to gross bowel obstruction in 22 (31%) and mild degree in 15 (21%). A soft tissue shadow suggestive of intussusception was found in 35 (49%). Intussusception was diagnosed on admission in 63 (88%) cases, and in the rest the diagnosis was delayed beyond 24 hours. The χ^2 test, or where appropriate, Fisher's exact test were used to assess significance.

Results

After adequate resuscitation with half strength dextrose-saline or plasma, or both, barium enema reduction was attempted in 65 cases (90% of the total). Diazepam and hyoscine butylbromide in the appropriate dosage were given for sedation and bowel relaxation, respectively (diazepam 250–300 μg/kg by slow intravenous injection, hyoscine butylbromide 400 μg/kg by slow intravenous injection). In the other seven cases, barium enema was not attempted (three because of previous recurrence, three because of very gross bowel obstruction, and one because of the choice of the attending surgeon). Forty nine cases out of the 65 attempts were successfully reduced, and two more cases that were thought to be incompletely reduced were found to be completely reduced at laparotomy. The barium enema therefore completely reduced the intussusception in 51 of the 65 attempts, a success rate of 79%. There were five recurrences, and two were in one patient. The interval between the reintussusception varied between one month and eight months with an average of about three months. The recurrence rate was 10% (5 out of 51).

Twenty five cases were subjected to operation (14 after failed hydrostatic reduction, two after presumed failed hydrostatic reduction, seven who did not have reduction with barium enema attempted, and two because of suspicion of non-Peyer's patch lead points even after successful reduction). Gut resection was carried out in three cases, one because of Meckel's diverticulum and two because of gangrenous bowel. One patient with failed barium enema reduction was shown at surgery to have a volvulus of the small bowel associated with malrotation proximal to an intussusception, which was easily reduced. The intussusception was thought to have predisposed the volvulus.[1] There was one late recurrence after operation. This occurred in the same patient who had previously had two recurrences after successful barium enema reductions. Complications included two wound infections, one chest infection, and one postoperative bowel obstruction due to adhesions.

Analysis of the successful and failed barium reductions showed that age group did not seem to be a significant factor (Figure). Those cases with rectal bleeding, signs of shock, duration of symptoms for more than 48 hours, and a pronounced degree of bowel obstruction had a poorer chance of successful reduction. The Table shows that the presence of rectal bleeding or shock on admission did not achieve significance. There was, however, a much larger percentage of patients with symptoms longer than 48 hours in the failed group than in the successful group (χ^2=0·06, df=1, p<0·01). Also, a pronounced degree of bowel obstruction was related to a failed reduction (χ^2=11·93, df=1, p<0·001).

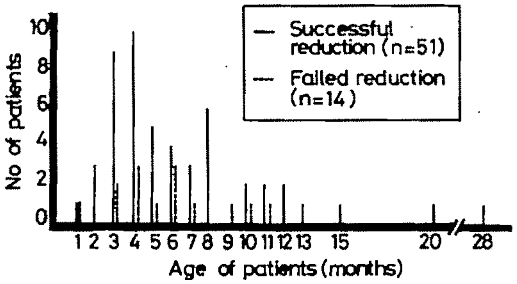

Figure *Age of patients in the groups with successful and failed barium enema reductions.*

Table *No (%) of patients with signs and symptoms in the groups with successful and failed barium enema reductions*

Signs and symptoms	*Group with successful reduction (n=51)*	*Group with failed reduction (n=14)*
Symptoms >48 hours*	3 (6)	5 (36)
Rectal bleeding	33 (65)	12 (86)
Shock on admission	2 (4)	2 (14)
Pronounced degree of bowel obstruction**	9 (18)	9 (64)

*p<0·01; **p<0·001.

There was no mortality in this series treated either by operation or with barium enema reduction. Apart from the 10% recurrence rate in the cases treated with barium enema reduction there was no other morbidity, whereas there was a small but definite morbidity in the group treated by operation. This might be due to the poorer condition of the cases chosen for operation. The duration of stay in hospital also differed significantly, being 8½ days in the group treated by operation and 3½ days in the group treated with barium enema reduction.

Discussion

The use of barium enema reduction has become increasingly the method of choice in the treatment of intussusception. The success rate varies in different centres from 18% to 85%.[2–9] In our series a success rate of 79% of those attempted was obtained. This represents a success rate of 70% overall.

It has been considered that barium enema reduction should not be attempted in patients whose duration of symptoms is greater than 24 hours and who are very ill.[10 11] Yet we had nine patients whose symptoms were longer than 24 hours, two patients with symptoms greater than 48 hours, one patient with symptoms over 72 hours, and two cases presenting in shock, and all of them were successfully reduced with barium enema. In such cases, however, there is a poorer prospect of reduction, and they should be approached with extra caution as being at greater risk of the disaster of perforation during barium enema.[12 13] The only absolute contraindication to attempted hydrostatic reduction, in our opinion, is evidence of peritonitis or pneumatosis intestinalis (none in our series) provided that the following principles are strictly observed:

1. A paediatric radiologist is readily available.
2. The facility of image intensification and timer is available.
3. Adequate resuscitation of the patient.
4. Ready access to operative intervention if hydrostatic reduction fails.
5. Recurrence more than once calls for operation reduction.

One objection to hydrostatic reduction is the radiation involved. Most reductions take only seven to eight minutes' screening time, and with the low radiation factors possible with image intensification and a small field the level of irradiation seems acceptable. Problems that may arise from using barium enema reduction include perforation of the colon, reduction of non-viable bowel, incomplete reduction, missed reduction of a non-Peyer's patch lead point, and delay of operative treatment in the unsuccessful cases. Perforation of the colon is very rare.[12 14] No rupture of the bowel was encountered in our series. From our experience perforation is unlikely to occur if the barium receptacle is no more than one metre higher than the table. Attempts at reduction are abandoned if the condition of the child is poor, if more than 15 minutes fluoroscopy is required, or if the head of the intussusception remains stationary for ten minutes as shown by occasional screening. Reduction of non-viable bowel does not seem to occur with the moderate hydrostatic pressure employed. Incomplete reduction is unlikely if it is mandatory that free reflux is observed into the small bowel. In fact, even when no free reflux took place, reduction was later shown to be complete either at operation (two cases) or repeat barium enema (nine cases). This is probably explained by decreasing oedema in the bowel and at the ileocaecal valve[15] and by the effect of the relaxants.[9] Thus provided that the clinical condition of the patient is satisfactory, and repeat barium enema is readily available, complete reduction can be confirmed or further reduction attempted. The incidence of aetiological lead points other than Peyer's patch is low in most series.[7 9] In our series only one patient had a lead point of aetiological importance. The only causative lesion of concern is lymphosarcoma, which usually causes chronic intussusception[3 7] and is unlikely to be missed. Significant delay of operative treatment in those unsuccessful cases should not occur if facilities for operation are readily available.

Our study thus favours the use of barium enema reduction in the treatment of intussusception, as the complication rate is low, the duration of hospital stay is shorter, and the child is spared an operation.

We thank our surgical colleagues for permission to review their patients and acknowledge the help of Dr Leslie Daly of the Department of Community Medicine, University College Dublin, for review of the statistics.

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Short reports

Cause of neonatal convulsions

Towards more precise diagnosis

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SUMMARY All infants presenting with neonatal seizures over a two year period were carefully investigated for the cause. In 20% either intracranial haemorrhage or infarction of a major cerebral artery was detected by real time ultrasound. Routine imaging techniques should be performed in all infants with neonatal convulsions.

The incidence of neonatal convulsions varies between 1·5 and 14 per 1000 liveborn infants.[1 2] Although a large number of aetiological factors have been implicated, few studies have reported the various causes among a cohort of newborn infants. We prospectively studied all infants with neonatal seizures over a two year period by a variety of investigations, including high resolution real time ultrasound, and found intracranial haemorrhage to be an important and relatively frequent finding.

Patients and methods

Over a two year period all infants with clinically observed convulsions were carefully investigated. Infants of 35 weeks' gestation and above were included in the study if they had been witnessed to have a convulsion by a member of the medical staff. Seizures occurring at any time from birth to the 28th day of life were considered. Those infants referred from outside the hospital were included if they fulfilled the above criteria.

Initial investigations included blood sugar, serum electrolytes, including calcium, blood cultures, and a real time ultrasound examination of the brain (ATL 300i machine fitted with a multifrequency transducer). In addition the labour ward records were examined for evidence of fetal distress on cardiotachograph recordings and the Apgar scores were noted. For a diagnosis of asphyxia to be made, the infant was required to show some evidence of distress in utero or at birth, and also to show the classic progression of neurological abnormality associated with this condition.[3] If these criteria were normal or if the infant continued to have convulsions then the following investigations were also performed: TORCH screen (antibody titres for toxoplasmosis, rubella, and herpes; urine microscopy for intracellular inclusion bodies), lumbar puncture, urine for amino acid and organic acid chromatography, and a 'metabolic' screen of urine for reducing substances, pH, ketones, sugar, and glycosaminoglycans.

Results

Sixty one infants were studied. Gestation ranged from 35 to 42 weeks (median 40), and the time of the first convulsion ranged from 2 hours to 25 days of age (median 2 days). A cause was evident in 56 (92%) of the infants (Table). The commonest cause was asphyxia (53%) but others were infection (8%) and metabolic (5%), hypoglycaemia (3%), and congenital abnormalities (3%). Three infants were found to have neonatal 'stroke' and nine had intracranial haemorrhage. The varieties of haemorrhage included intraventricular (4 cases), thalamic (2 cases), primary parenchymal, subarachnoid, and subdural associated with a tear of the tentorium (1 case each). Cerebral artery infarction affected the posterior cerebral artery in two cases (Figure) and the middle cerebral in one. Other disorders included maple syrup urine disease, hypernatraemia, and

Table *Causes (where determined) of neonatal convulsions in study infants*

Asphyxia—Intrapartum	28
Postnatal	4
Infection	5
Metabolic	3
Haemorrhage	9
Stroke	3
Congenital abnormality	2
Hypoglycaemia	2
Hypocalcaemia	0
Unknown	5
Total	61

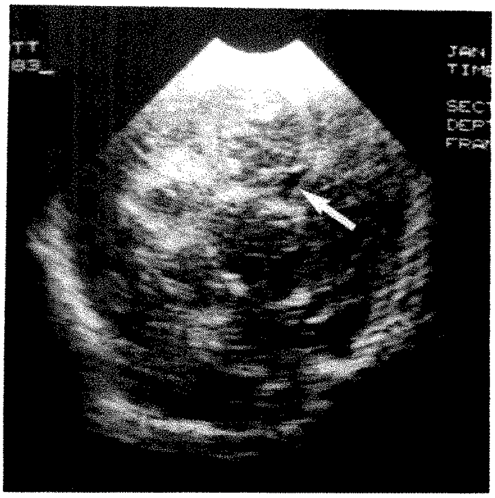

Figure *Posterior coronal scan showing slight shift of the midline towards the right with a normal right lateral ventricle (arrowed). There is a diffuse area of increased echodensity obscuring the ventricle on the left side corresponding to the area of infarction.*

accidental ergometrine injection at birth. No infants had hypocalcaemia as the primary cause of their seizures. Congenital abnormalities included holoprosencephaly and spina bifida with hydrocephalus. Both infants with hypoglycaemic convulsions had major underlying pathology (congenital heart disease in one and trisomy 9 in the other). Of the five infants in whom no cause could be found, a single seizure occurred in one on the first day of life and in another multiple convulsions developed on day 10. Three babies had seizures on days five or six; these were self limiting and the infants seemed to be neurologically normal between seizures.

Discussion

Two recently reported studies found no definite cause for neonatal convulsions in 29%[1] and 69%[4] of term infants. The latter study of Goldberg reported that 52% of all infants born at term and admitted over a 10 year period had so called 'fifth-day fits'. As there is no satisfactory explanation for these seizures it seems more appropriate for the present to refer to them as being of unknown origin. Only three infants in our study would fall into this category.

Intracranial haemorrhage or neonatal stroke seems, in our study, to have a common and important association with neonatal seizures, accounting for 20% of the total cases. We cannot be certain that haemorrhage was the cause of the seizure in all cases but it is very unlikely that the convulsion caused the intracranial bleed. It is possible that a more fundamental insult caused both seizures and haemorrhage. Nevertheless intracranial haemorrhage seems to be a useful marker for such cerebral injuries and a prognosis may be given on the basis of this condition.

There have been four studies in the past 10 years reporting the incidence of different causes of neonatal fits.[1 4–6] Three do not report intracranial haemorrhage to be a cause in any cases and the fourth[4] detected haemorrhage as the cause of seizures in only 2·5% of cases. None of these studies seemed to use any form of imaging technique. In a recent study Fenichel and colleagues[7] reported 22 term infants with intracranial haemorrhage, of whom 18 (82%) developed seizures in the neonatal period. In addition, a French study described eight infants with neonatal stroke, and seizures occurred in all.[8] It is likely that both intracranial haemorrhage and neonatal stroke occur frequently in newborn term infants and present very commonly with seizures.

In summary, we have shown that haemorrhagic or infarctive lesions of the neonatal brain are a relatively common cause of neonatal seizures. Real time ultrasound is a very reliable method of diagnosing these conditions[9] and this investigation should be part of the routine screen of all infants with seizures.

Dr J Q Trounce is supported by the Spastics Society.

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Neonatal respiratory distress due to mumps

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SUMMARY We report an infant of 35 weeks' gestation who developed severe respiratory distress and pneumonitis due to perinatal mumps virus infection.

It is unusual that mumps virus should be responsible for neonatal respiratory distress. To our knowledge only one case has been described.[1] We report a case in which infection was probably transplacentally acquired and resulted in severe pneumonitis.

Case report

A male infant was born at 35 weeks' gestation weighing 2530 g after a normal pregnancy. After spontaneous rupture of the membranes, delivery was induced after a rise in temperature to 38·5°C. Given the risk of infection, the child, whose results of clinical and bacteriological tests were normal, was treated with antibiotics. On the third day of life his temperature rose to 38·5°C. On the sixth day oral feeding was stopped because of bilious gastric aspirates and abdominal distension and replaced with parenteral nutrition. On the seventh day tachypnoea and cyanosis developed. A chest *x* ray film showed irregular opacities. On day 13 hepatomegaly, tachycardia, and coughing were observed. Echocardiography was normal. The persistence of severe respiratory distress necessitated endotracheal intubation and mechanical ventilation. Six days later the child's state improved rapidly, allowing extubation. Oral feeding was started again. Antibiotics were carried on for 23 days. Results of a hearing test by an auditory cradle were normal, and the child was discharged. He was seen again one month later and showed no further symptoms.

Bacteriological cultures of blood, faeces, urine, and tracheal excretions and from the umbilical catheter were negative. Cerebrospinal fluid colected on days 2, 6, 17, and 23 was normal. Plasma amylase activity was 700 U/l, 10 times the normal, with normal plasma lipase activity. Blood count on day 8 was haemoglobin 154 g/l, white blood cell 5×10^6/l ($2·6\times10^6$ polymorphonuclear leucocytes and $2·2\times10^6$ lymphocytes), and on day 14 was haemoglobin 124 g/l, white blood cell 20×10^6/l ($11·3\times10^6$ polymorphonuclear leucocytes, $7·3\times10^6$ ymphocytes, and $1·8\times10^6$ monocytes). Mumps virus was isolated from a throat swab taken on day 9. A significant rise in mumps antibodies was shown by complement fixation test and by an indirect enzyme linked immunosorbent assay (ELISA test) for the presence of IgM antibodies (see Table). No mumps virus antibodies were found in the cerebrospinal fluid. On day 24 tests for mumps virus antibodies were carried out on the child's family: the mother had high antibody concentrations of IgM and IgG classes, and a 4 year old brother had high concentrations of IgG antibody only.

Table *Isolation and serology of the mumps virus on the patient and his family*

	Patient		*Mother*	*Brother*	*Father*
Day	*10*	*24*	*24*	*24*	*24*
Mumps virus isolation	+	–	–	–	–
Mumps antibodies tests:					
Complement fixation	1/32	1/256	1/192	1/96	1/32
Indirect IgG	1/128	≥1/2048	≥1/2048	≥1/2048	1/128
*ELISA IgM	1/512	≥1/1024	1/128	Negative	Negative

*ELISA=Enzyme linked immunosorbent assay.

Comment

This neonate showed an unusual response to mumps virus infection shown by severe respiratory distress and pneumonitis without parotitis. The mother had no obvious signs of mumps infection during pregnancy, but latent or unusual forms of infection are common. The presence of high concentrations of mumps antibody with IgM specificity allows a rough dating of maternal infection to the last weeks of pregnancy or at delivery. Fever at this time may be the only clinical sign of a primary mumps infection. The mother probably acquired her infection from her first son who had high IgG antibody concentrations. The baby may have been infected transplacentally because the delay of three days before the onset of the disease is considerably shorter than the incubation period.

Mumps virus can cross the placenta: it has been isolated from a 10 week old fetus spontaneously aborted after maternal mumps parotitis.[2] The incidence of mumps infection has been variously estimated as between 0·8 and 10 cases per 100 pregnancies.[3] During mumps, virus initially replicates in the epithelium of the upper respiratory tract. A viraemia follows, and there is often prolonged excretion of virus in the urine for two to three weeks. Only six cases of mumps virus infections occurring at the end of pregnancy have been described.[3 4] Four infants developed a parotitis during the first week of life, one child remained asymptomatic, and no virus was isolated. One child was admitted on the seventh day of life with high fever and respiratory distress, which resulted in a week of ventilation.[1] The outcome was good and one year later the child was still well. Common features with our case were general illness, respiratory distress, latent period, and good prognosis after symptomatic treatment.

Mumps infection in the newborn can be misleading because of the lack of apparent parotitis or meningitis. It emphasises the value of systematic early virologic studies in any neonatal infection.

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Comparison of ultrasound examination and intravenous urography after a urinary tract infection

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SUMMARY The results of ultrasound examination and intravenous urography after a urinary infection were compared in 100 children. Thirty seven had an abnormality on urography, but in 12 this was not seen on ultrasound. One of these had renal scarring, the remainder only minor abnormalities.

Investigations after a urinary tract infection are carried out to detect factors predisposing to infection (obstruction lesions and gross vesicoureteric reflux) and early renal scarring. Until recently this involved an intravenous urogram (IVU) and micturating cystourethrogram in all children after the first infection.[1] These investigations involve irradiation, are unpleasant, and have potential complications. A selective approach has been advocated with an IVU in all cases, a micturating cystourethrogram being deferred until a second infection in children with a normal IVU.[2] This still means that an IVU is carried out on all children with an infection. Ultrasound examination is painless, free from side effects, and would be an acceptable alternative investigation if the abnormalities mentioned above could be reliably detected. A preliminary report comparing ultrasound and IVU in children with an infection showed only a small number (10%) of false negatives.[3] The age of the patients, however, was not given, and, as the risk of renal damage is much higher in young children,[4] this is important. We report a study comparing ultrasound examination and IVU in 100 children, 59 of whom were under 5.

Material and methods

One hundred children, 71 girls and 29 boys, were investigated after a urinary tract infection. The diagnosis of infection was based on urine culture showing 10^5 or more organisms per ml. Eleven were aged under 1 year, 48 between 1 and 5, and 41 over 5.

The renal tract of each child was imaged with ultrasound and then immediately afterwards by an IVU.

All ultrasound examinations were performed by one radiologist (DL) using the 5 MHz probes of the Hitachi EUB-25 linear array scanner and the ATL mark 300 sector scanner. The kidneys were assessed for congenital anomalies and for evidence of renal scarring. Dilatation of the distal ureters was looked for closely as this might suggest reflux. If possible the pelvis was scanned when the bladder was full.

After the ultrasound examination an IVU was performed using iopamidol (Niopam 300) in a dose of 2 ml/kg. The number of films taken at each examination varied and was kept to the minimum that showed the renal outlines clearly, an opacified pelvicalyceal system, and a reasonably full bladder. In addition to structural abnormalities of the renal tract and evidence of renal scarring, particularly close attention was paid to changes such as minor calyceal blunting and ureteric dilatation that might suggest vesicouretric reflux.

The result of the ultrasound examination was reported first, and then compared with the IVU.

Results

The Table presents the results separately for the three age groups. Of the 11 babies aged under 1, eight (73%) had an abnormality on both ultrasound and IVU; the remaining three were normal on both examinations. Of the 48 children aged 1–5, 18 (38%) had an abnormality on IVU, but in seven this was not seen on ultrasound. In the 41 children over 5, 11 (27%) had an abnormality on IVU, but in five this was not seen on ultrasound. Thus there were 12 false negative results in 100 children on ultrasound examination compared with IVU. One was a 6 year old girl with bilateral scarring who had had at least two infections. Doubtful unilateral scarring was found in a 3 year old girl whose IVU showed a slightly irregular lateral margin of the left kidney. The calyces were normal, and this may have been fetal lobulation. Thus only one potentially serious condition was missed on ultrasound examination of these children. A further seven cases of scarring were detected on ultrasound examination, giving a false negative rate for renal scarring of 12%. There were no false positives on ultrasound examination.

Table *Abnormalities on IVU and ultrasound in 100 children after a urinary infection*

	Present on IVU	*Present on ultrasound*	*Not seen on ultrasound*
Hydronephrosis:			
With obstruction	7	7	0
Without obstruction	1	1	0
Renal scarring	9	7	2
Minor calyceal blunting	8	2	6
Dilated ureter	4	1	3
Calculus	3	3	0
Malrotation, dysplasia, absent kidney	4	4	0
Hemivertebra	1	0	1
Total	37	25	12 (false negatives)

Discussion

Most abnormalities that were not detected on ultrasound examination were cases of minor calyceal blunting, the importance of which is unclear, or mild ureteric dilatation, which is probably of no clinical importance. Obstructive lesions, which are surgically correctable, were reliably detected. Ultrasound examination detected seven out of eight definite cases of renal scarring, a false negative rate of 12%.

On the basis of our results we feel that in children aged over 1 routine IVU, after a first urinary tract infection, with its possible risks and undoubted unpleasantness could be replaced by ultrasound examination. A plain *x* ray film of the abdomen should be performed as ultrasound does not always detect calculi or skeletal abnormalities. If the child has a further infection an IVU could then be performed. In this way renal scarring that will have been missed in a few cases initially will be detected. The renal damage caused by a single further infection in a child with scarred kidneys is probably small as most damage has occurred by the time the child first presents,[5] and we think this is an acceptable price for saving 50% of children with a urinary tract infection from IVU.

The kidneys of infants aged under 1 seem to be more vulnerable to scarring than older chiildren.[6] IVU often fails to show the renal outline, due to the lower glomerular filtration rate, and so scarring is difficult to detect. Ultrasound examination to detect obstructive lesions and micturating cystography to detect severe reflux, with the potential of intrarenal reflux and renal scarring, would be logical investigations at this age. Any abnormality could be further defined by renal scintigraphy.

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Suction biopsy in Hirschsprung's disease

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SUMMARY Seventy two children with symptoms and signs consistent with Hirschsprung's disease had full thickness and suction rectal biopsies performed. Results were identical with both methods, except for one case of total aganglionosis of the colon. Full thickness biopsy no longer has a place as a screening method.

In the management of chronic constipation Hirschsprung's disease may be diagnosed on the basis of radiological investigation, anorectal manometry, and rectal biopsy. Though *x* ray films and manometric studies may be highly suggestive, the definitive diagnosis requires rectal biopsy.[1 2]

The classical method of rectal biopsy involves taking a full thickness of rectal mucosa and underlying muscle, requiring general anaesthesia and suturing of the biopsy wound. The possible complications necessitate inpatient management, and its morbidity precludes its use as a screening procedure.

The introduction of suction rectal biopsy of mucosa and submucosa represents a considerable advance.[3 4] Biopsy requires neither general anaesthesia nor suturing, may be carried out even on outpatients, is suitable for all ages, and rarely leads to complications.

Several teams have reported false negative results when compared with full thickness biopsy.[5] We investigated over 2000 children with chronic constipation and suspected Hirschsprung's disease and performed suction biopsies on 400 of them. To assess the validity of the suction results we are reviewing all the cases (72) in which full thickness biopsies were also carried out, either at a formal resection or at upper partial sphincterotomy.

Patients and methods

Suction biopsy specimens were taken from 72 patients aged from a few weeks to 17 years. They were suspected of having Hirschsprung's disease. Some biopsy specimens were taken without anaesthesia and others under general anaesthesia just after manual evacuation, anorectal manometry, or anal dilatation. Biopsy specimens were taken from the posterior wall of the rectum at intervals of 2, 3, 4, and 5 cm from the anal verge with a Quinton multipurpose biopsy machine.

These patients either came to formal bowel resection or, on failing to improve after repeated anal dilatations, received a therapeutic extended upper partial internal sphincterotomy, during which a full thickness biopsy specimen was taken from the edge of the wound before suturing the mucosa.

All biopsies, full thickness or suction, were treated in the same manner. After orientation, they were frozen in Iso-pentane cooled in liquid nitrogen before 8 μ sections were cut on a cryostat. Sections were stained with a modified Karnovsky-Roots technique[3] and also with routine haematoxylin and eosin stains. The tissues were then fixed in 10% formol saline, and serial sections of paraffin blocks were examined for the presence of ganglion cells. In some of the suction biopsy specimens in which enough submucosa was included ganglion cells could be seen in some of the sections.

A diagnosis of Hirschsprung's disease was made if larger than normal nerve fibres in increased numbers were seen in the lamina propria and muscularis mucosae at suction biopsy. At full thickness biopsy not only were the nerve fibres in the lamina propria and the muscularis mucosae assessed, but the presence or otherwise of ganglion cells and the size of the nerve trunks in the submucosal and intermyenteric plexuses were also assessed. All sections were examined by the same histopathologist without reference to previous biopsies.

Results were correlated independently by another person, and no patients who had had both sorts of biopsy were excluded.

Results

Seventy two patients were analysed. Of these, 54 showed normal nerve fibres on suction biopsy. In eight serial sectioning showed ganglion cells in the submucosa. Full thickness biopsy specimens showed normal nerve bundles and ganglion cells in the submucosal and myenteric plexuses. In 17 cases, cholinesterase staining showed an increased size and number of cholinergic nerve fibres both in the lamina propria and the muscularis mucosae at suction biopsy. In addition, full thickness biopsy specimens showed the typical hypertrophied nerve trunks of Hirschsprung's disease in the submucosal and intermyenteric plexuses. Serial sectioning failed to show any ganglion cells. The suction biopsy diagnosis of Hirschsprung's disease was confirmed in every case at full thickness biopsy.

In one further case, normal cholinergic nerve fibres in the lamina propria and muscularis mucosae were seen at suction biopsy and no ganglion cells could be identified in the small amount of submucosa present in the biopsy specimen. The clinical course, however, demanded further investigation. Serial sections of full thickness specimens sampling the whole colon, including the ileocaecal junction, failed to show any ganglion cells, but the nerve trunks in the submucosal and intermyenteric plexuses were normal. A diagnosis of total aganglionosis of the colon (Zeulzer-Wilson syndrome) was made.[6]

Discussion

Suction rectal biopsy has been used as a screening method for patients with symptoms and signs suggestive of Hirschsprung's disease in this department for six years. It has proved to be a more accurate screening method than radiology and/or anorectal manometry. There were no false negative or false positive diagnoses in 17 cases of Hirschsprung's disease, but full thickness biopsy was required to make the diagnosis of total aganglionosis in one case of non-Hirschsprung's constipation.

A review of the anorectal manometry on some of the patients shows the typical lack of reflex inhibition seen in Hirschsprung's disease but repeated suction and full thickness biopsies failed to show any histological abnormality. These are a 'physiological' or 'pseudo-' Hirschsprung's disease and respond well clinically to sphincterotomy. It is therefore essential that any patient suspected of having Hirschsprung's disease on anorectal manometry be submitted to rectal biopsy to confirm the diagnosis.

In the screening of patients with chronic constipation for Hirschsprung's disease, suction biopsy is as accurate as full thickness biopsy. It should be accompanied by anorectal manometry for more detailed analysis. Providing facilities for histochemistry are available, full thickness biopsy need have no further place as a screening method.

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Acquired toxoplasma encephalitis

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SUMMARY Toxoplasma was the cause of encephalitis in a 4 year old boy. He recovered completely after treatment with pyrimethamine and sulphadimidine. Toxoplasma encephalitis has a high mortality, and active treatment is recommended.

In childhood encephalitis it is unusual to discover a treatable cause. I report a case of encephalitis in which there was serological evidence of a toxoplasmic aetiology.

Case report

A 4 year old boy was well until October 1983 when he had a generalised convulsion. Three weeks later he began to have recurrent convulsions, which increased in frequency, and he became ataxic. On transfer to Sheffield in mid-December he seemed to be fully orientated, but had gross truncal ataxia, bilateral intention tremor, and dysarthria, although no nystagmus. There was no evidence of raised intracranial pressure, cranial nerve palsy, or limb weakness. He was receiving sodium valproate and phenytoin.

Table *Toxoplasma serology results*

Date	*Reciprocal titres*			*Specific IgM*
	Latex	*HA**	*Dye*	*ELISA† (EIU‡)*
15 December 1983	2048	1024	2048	0
23 January 1984			1024	38 (Positive)
13 April 1984	256			

*HA=Haemagglutination antibody.
†ELISA=Enzyme linked immunosorbent assay.
‡EIU=Enzyme international units.

There was no abnormality on computed tomography or examination of cerebrospinal fluid. An electroencephalogram in October had been normal, but a further electroencephalogram now showed disintegration of the background rhythm with generalised bursts of spike activity, suggestive of encephalitis. Investigation revealed no evidence of a neurodegenerative disorder or metabolic abnormality. Blood concentrations of anticonvulsants were below normal therapeutic ranges. The only positive finding on paired viral serology was a rise in adenovirus titre from 1/10 to 1/40. Toxoplasma serology was as shown in the Table.

Before the first toxoplasma result and drug concentrations were known, it was suspected that he was suffering from drug toxicity. In view of his severe condition and frequent convulsions, therefore, previous drugs were withdrawn and prednisolone 40 mg/day and phenobarbitone were started, producing a dramatic reduction in convulsions and ataxia within three days. As the dose of prednisolone was reduced, however, both convulsions and ataxia recurred, and the convulsions began to assume a myoclonic nature. For several days he was drowsy with almost continuous myoclonic jerking. On receipt of the initial toxoplasma serology result, treatment with pyrimethamine, sulphadimidine, and calcium folinate was begun. After two weeks of this treatment he began to improve and then rapidly returned to normal, although some myoclonic convulsions continued until clonazepam was added.

After six months, anti-toxoplasma treatment and anticonvulsants were withdrawn, and he has remained well. Electroencephalograms after three and a half months' and six months' treatment showed progressive improvement, although some right sided predominance remained.

Discussion

Acquired toxoplasmic encephalitis in childhood was first reported in 1941.[1] In recent years toxoplasmic encephalitis has become a recognised opportunistic complication of a variety of immune deficient states,[2] but of 45 published cases of acquired central nervous system (CNS) toxoplasmosis reviewed by Townsend *et al* in 1975, 22 had no known pre-existing immune deficiency.[3]

The manifestations of CNS toxoplasmosis vary considerably, from non-specific encephalopathy or diffuse meningoencephalitis to features of space occupying lesions.[3] Cerebrospinal fluid pleocytosis is not invariable.[4]

In this case the high initial toxoplasma latex titre with subsequent fall, the conversion of the specific IgM ELISA test during the illness, and the response to anti-toxoplasma treatment provide convincing evidence of an acute toxoplasma infection, which was probably the cause of the encephalitis. The rise in adenovirus titre was probably related to a minor intercurrent illness.

The usual course of acquired toxoplasmosis without CNS involvement is spontaneous recovery, but published reports suggest that when the CNS is involved there is a high mortality.[3 4] We recommend, therefore, that evidence of toxoplasma infection be sought in every case of unexplained encephalitis, and that, when found, the condition should be treated actively with pyrimethamine and a sulphonamide. Calcium folinate may be given simultaneously to prevent haematological side effects of pyrimethamine. Although steroids were given in this case before diagnosis, in toxoplasmosis they may be deleterious and should be avoided. There are no clear guidelines on duration of treatment, but it was decided to treat this boy for six months, as recommended by Luft *et al*,[4] and no adverse effects of treatment were observed.

I thank Dr B L Priestley and Dr J M Davies for permission to report this case, which was under their care.

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Immunoglobulin for neonatal agranulocytosis

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SUMMARY An infant with an alloimmune agranulocytosis whose granulocyte count temporarily returned to normal during intravenous, high dosage immunoglobulin treatment is described.

Agranulocytosis and profound neutropenia in the neonatal period is a serious condition associated with high mortality. Most patients develop fever associated with skin infections, pneumonia or septicaemia, or both, within the first days of life. The infections are predominantly caused by *Staphylococcus aureus*, and less often by *Escherichia coli* or β haemolytic streptococci. Prophylaxis with antibiotics has been recommended for these infants.[1]

A boy with neonatal agranulocytosis was investigated. It was considered that the cause was probably an alloantibody on the boy's neutrophils directed to parental antigen. Treatment with high dose intravenous immunoglobulin temporarily restored his neutrophil count.

Case report

This boy was born at 39 weeks' gestation and weighed 3·6 kg. He is the second child of healthy, unrelated parents. At age 3 days, a pemphigoid exanthema developed, and *Staphylococcus aureus* was cultured. Cloxacillin was given intravenously, and during the following days the lesions healed. Fever (39°C) was observed on day 10 and the boy

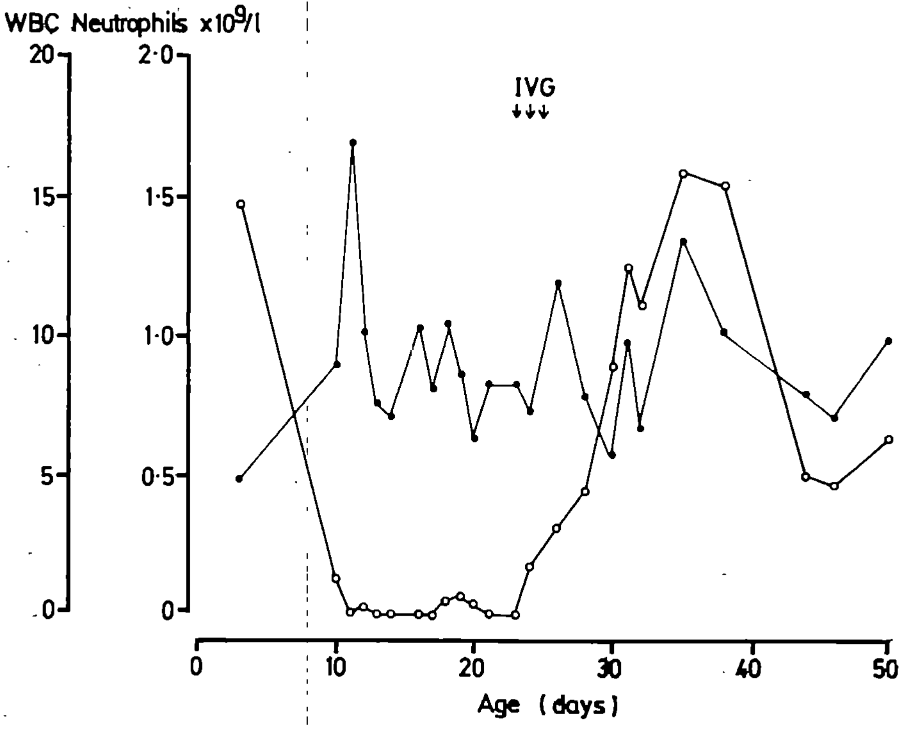

Figure *Neutrophil count and white blood count (WBC) during the first 50 days of life.*

Intravenous immunoglobulin (IVG) was given for three consecutive days. Lowest border of normal range for neutrophils are: Cord blood 5·5×10^9/l; at 12 to 24 hours of age 10×10^9/l; at 72 hours of age 2·5×10^9/l, and from 1 month of age 1·5×10^9/l.
○=neutrophils; ●–WBC.

was again started on intravenous antibiotics (ampicillin and netilmicin). His white blood count on days 7 and 10 showed a progressive neutropenia (Figure) and repeat determinations over the following days showed agranulocytosis. Antibiotics were stopped and the child was referred to this hospital. Prophylactic co-trimoxazole was given. A bone marrow aspirate showed normal cellularity and normal myelopoiesis. In vitro tests for cellular immunity gave normal values for T cells and B cells, and the lymphocytes responded normally to mitogens. IgG was 5·6 g/l, IgA 0 g/l, and IgM 2·4 g/l at 3 weeks of age. Leucocytagglutinin tests were repeatedly positive. Further testing using serum from the child and the mother and white blood cells from the father showed that the mother had a cytotoxic antibody to HLA-A24 bearing cells, an HLA antigen common for the father and the elder sister, but not the patient. The serum of the mother and the infant also contained an antibody that reacted with the father's granulocytes. The antibody was not further defined regarding its specificity for the granulocyte antigens NA1 and NA2. Serum from the child did not agglutinate the mother's granulocytes. Subcutaneous adrenalin increased the white blood count from $7\cdot1\times10^9$/l to $22\cdot3\times10^9$/l, but failed to liberate any neutrophils.

Intravenous immunoglobulin

Because of the possibility of further serious infections, and after informed consent from the parents, it was decided to treat the child with high dose intravenous immunoglobulins. Gammonativ (Kabi-Vitrum, Sweden), a native human immunoglobulin prepared according to the Cohn method and stabilised with an equal amount of human albumin, was given according to the regimen proposed by Imbach for immune thrombocytopenia (400 mg/kg for five consecutive days).[2] For convenience, however, the total dosage was given within three consecutive days instead of five. In the next 11 days the granulocytes rose to $1\cdot6\times10^9$/l (Figure), later declining to values varying between 0·3 and $0\cdot7\times10^9$/l for the next eight weeks, without any further infectious episodes. Thereafter the neutropenia gradually returned to normal and remained well above 1×10^9/l from the patient's 16th week of life.

Discussion

Neonatal neutropenia is most commonly caused by acquired bacterial or viral infections. Acquired neutropenia is usually of short duration, however, and is seldom profound. Agranulocytosis points to other underlying diseases either of the haematopoetic stem cell or the granulocyte progenitor, or to diseases associated with an abnormal peripheral neutrophil destruction. Progenitor disease was ruled out by normal habitus, normal bone marrow smear, and normal specific immunology. Alloimmunity to paternally inherited granulocyte antigens was found to be the likely cause. It is a very rare but well defined cause of neonatal neutropenia,[1] which should resolve in two to 17 weeks. Plasma exchange followed by infusion of maternal granulocytes has been suggested as treatment in cases of life threatening infections.

In immune thrombocytopenia Imbach and coworkers[2] showed that it was possible to treat and obtain a cure with high dose intravenous immunoglobulin treatment. Many recent reports confirm their finding, and this mode of treatment has also been applied successfully to alloimmune neonatal thrombocytopenia.[3]

The response to intravenous immunoglobulin in immune thrombocytopenia is most favourable in the acute form of the disorder. In chronic disease the results parallel those in our case—a prompt rise but one which only lasts for two to three weeks.

In this boy, immunoglobulin infusion resulted in a temporary return to normal of the granulocyte count over a time period corresponding to the expected half life for IgG of three weeks. This agrees with a recent report on immunoglobulin treatment for an immune neutropenia in older children.[4] High dose immunoglobulin treatment seems to be a safe and easy method of curing, at least temporarily, immune neutropenia, and covering a critical period of high risk for serious infectious complications. It should bear substantially fewer complications than plasma exchange. Intravenous immunoglobulin treatment is not, however, indicated in other forms of neutropenia, and should not be given to a newborn or any other child who just happens to be neutropenic.

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Personal practice

Inhalation treatment for asthma

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SUMMARY Inhaled medication has revolutionised the lives of many children with asthma. Despite this we see many children for whom appropriate inhaled medication has been prescribed but whose symptoms continue to be poorly controlled. In our experience this is often due to poor technique or inappropriately prescribed devices and an inadequate understanding of when and how to use the treatment. The prescribing physician must have a clear idea of the optimal inhalation technique. We have reviewed the standard devices available and our use of them in the treatment of childhood asthma.

Inhalation of potentially medicinal substances for chest problems has been advocated for hundreds of years,[1] but it is only in this century that the practice has evolved into an established treatment for asthma. The principle of delivering a drug selectively to the target organ, to be effective rapidly, in small doses, and with consequent minimal side effects has been a pharmacological ideal which ostensibly is easily achieved when applied to the respiratory tract. The respiratory tract, however, has several mechanisms that protect it from the entry and deposition of particles. Aerodynamic filtration, reflexes such as cough and sneeze, and mucociliary clearance all contribute to the rapid elimination of inhaled soluble and particulate materials.

How far particles penetrate into the respiratory tract is to some extent governed by their size. Those larger than 15 μm in diameter are removed by the coarse filter of hairs at the nares while particles more than 10 μm are deposited in the nose and nasopharynx where the total cross sectional diameter of the airway is small and consequently the air flow high. These large particles have enough inertia to cause *impaction* on airway walls when the air stream changes direction. Particles of 0·5 to 5 μm chiefly deposit by *sedimentation* as a result of gravitational forces in areas of low flow. There is a rapid increase in cross sectional area of the airways beyond the 10th bronchial division and consequently a rapid fall in air flow. Particles of less than 0·1 μm are deposited mainly as a result of *Brownian motion*, but particles between 0·5 and 0·1 μm are least effected by sedimentation or Brownian motion and only about 20% are retained in the lung, the rest being exhaled.[2]

The site and degree of deposition of particles may be further affected by reflexes such as cough and bronchoconstriction and by disease in the lower respiratory tract.[3] [4] The optimum particle size for the deposition of drugs seems to be about 2 to 10 μm, but while it is generally felt that large doses uniformly distributed through central and peripheral airways is an ideal for all inhaled medications, this is not established by objective evaluation. It is possible that different medications may be optimally placed in different areas, that is bronchodilators centrally in muscled airways and steroids peripherally in smaller airways most affected by mucosal oedema.

The method of production of aerosols and the mode of delivery influence the particle size presented to the airways and thus the amount of drug carried to different parts of the respiratory tract.[4] In about 1856, an 'atomiser' was designed to deliver medication by inhalation and soon became similar to modern jet nebulisers.[1] There are currently three main systems in use:

(1) Nebulisers;
(2) Metered dose inhaler aerosols (with or without spacer devices);
(3) Dry powder inhalers.

(1) Nebulisers

There are two varieties in clinical use, ultrasonic and jet nebulisers.

Ultrasonic nebulisers (Fig. 1). These generate an aerosol by the high frequency oscillation of a piezo-electric crystal close to the respiratory solution. This causes the fluid to break up into droplets that can be inhaled. The advantage of this type of nebuliser is that it is less noisy than jet nebulisers and will deliver a large quantity of liquid over a prolonged time (as needed in humidification). Disadvantages are that most are very expensive and require more care and maintenance than jet nebulisers. The only relatively cheap model requires the patient to breathe in actively to open a valve: this makes it unsuitable for children who may not generate enough force when unwell.

Jet nebulisers. (Fig. 2). These are most commonly used clinically in this country being cheaper than ultrasonic units. Many models are available but the mechanics are similar in all. A high velocity gas jet is blown through a fine hole, creating a negative pressure by the Venturi effect. This causes fluid to be drawn into the jet stream which is impacted on a baffle, breaking up the fluid into droplets. Large particles fall back into the reservoir while the smaller remain in suspension and may be inhaled. The energy for the jet may be generated from an air compressor or a cylinder of compressed air or oxygen. The many different nebuliser units have slightly different properties while the output of the nebulisers is influenced by the flow rate of the gas through them and the volume of liquid nebulised.[5] Although this is important in standardisation during clinical trials and bronchial provocation tests, it is unlikely to be as important in clinical practice as long as the general instructions for the device are followed,[6] but certain standards are recommended. A driving flow of more than 6 litres/minute and filling the chamber to 4 ml seems to be optimum to achieve output of particles less than 5 μm, to release 60 to 80% of the solution from the nebuliser, and to limit the time of nebulisation. Even with optimal use only about 12% of a nebulised solution is deposited in the lungs.[7] The speed of nebulisation of the medication may influence compliance, five to 10 minutes usually being acceptable. There is no information on whether faster nebulisation by more powerful machines is equally effective, provided an equal dose of drug is given. Several trials have shown an additional benefit of a second dose of bronchodilator some time after a first,[8] implying that a longer duration of administration may be better. The advantages of a nebuliser are that it needs little cooperation, requiring only tidal breathing. Some of the drugs can be mixed and taken simultaneously (for example salbutamol and sodium cromoglycate). Furthermore, oxygen can be used to drive the nebuliser and this may be important in severe asthma to avoid hypoxia. The disadvantages are that it is bulky, requires power (either from a compressed gas cylinder or from a compressor), and is relatively expensive (£35 for a foot pump com-

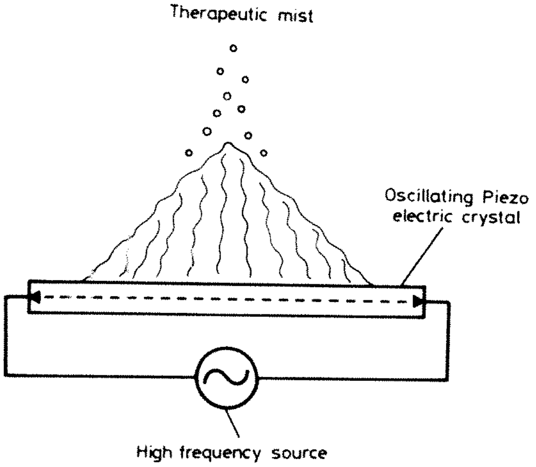

Fig. 1 *Ultrasonic nebuliser.*

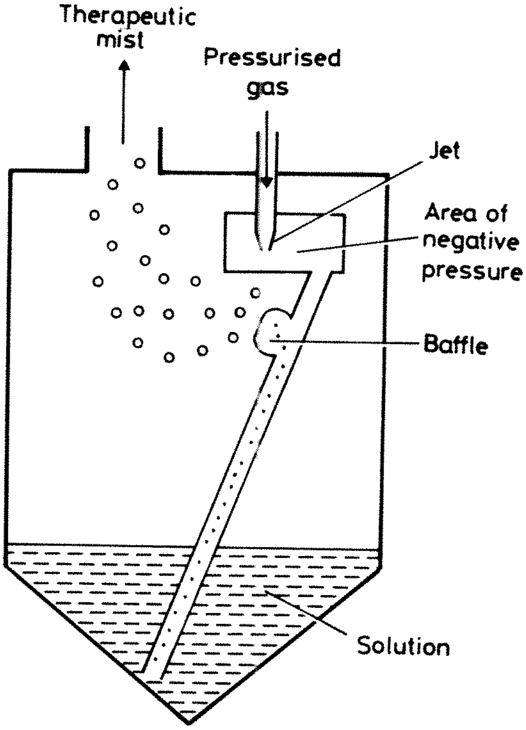

Fig. 2 *Jet nebuliser.*

pressor to £100 for a compact electric unit), although this is still very economical if its use prevents an admission to hospital. When issued for home use, regular maintenance must be organised. The cheaper foot pump compressor is slower in delivering the medication and needs attention and effort just when a parent is concerned with the child. A potentially serious disadvantage is the possibility that the use of nebulisers with bronchodilators at home may lead to delay in seeking appropriate medical help during severe exacerbations leading to an increase in mortality. A recent increase in asthma deaths in New Zealand has been attributed to this[9] and may be similar to the epidemic of deaths after the increased use of pressurised aerosols during the 1960s.

(2) **Pressurised aerosols** (Fig. 3)

These have been used to deliver bronchodilators to the lungs for about 25 years, and more recently other drugs active against asthma and even non-respiratory drugs have been available by this method (for example glyceryl trinitrate, ergotamine).[10] The active drug is suspended in approximately 10 ml of a fluorocarbon propellant at high pressure. When the aerosol is actuated, a metered amount of the fluid is ejected under pressure from a valve mechanism. The propellant safety has been investigated and confirmed in normal usage, although reservations exist when the aerosol is grossly misused.[11] When the aerosol is actuated and the mixture of drug and propellant leaves the cannister, there is a rapid phase during which about 20% of the propellant evaporates. Further evaporation occurs at a much slower rate as heat is acquired from the atmosphere. The droplets consist of the drug surrounded by a coating of propellant. Immediately after actuation the particle diameter is about 43 μm. This falls to 14 μm at 10 cm from the cannister, and when the propellant has evaporated completely it is 2·8 to 4·3 μm, although this may take several seconds.

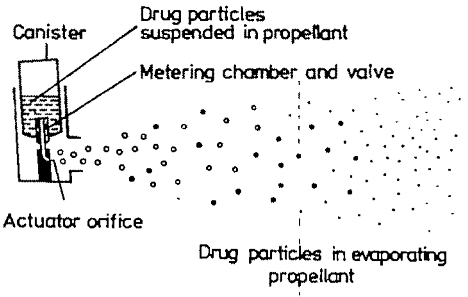
Drug particles suspended in propellant
Canister
Metering chamber and valve
Actuator orifice
Drug particles in evaporating propellant

Fig. 3 *Metered dose inhaler aerosol.*

The deposition of aerosols in the lungs has been investigated using radiolabelled teflon particles. With adults using a standard inhalation technique, 80% of the spray was deposited in the mouth, 10% remained in the actuator, 1% was exhaled again, and 9% remained in the lungs.[12] The importance of particle size on penetration to the small airways has been confirmed using terbutaline sulphate.[13] The effectiveness of the aerosol is considerably influenced by the technique and coordination during use. Actuation during inspiration, a full slow inhalation, and breath holding for 10 seconds at the end of inspiration all improve lung deposition, and thus increase forced expiratory volume in one second (FEV_1) rise if a bronchodilator is used.

The aerosol has the great advantage of being portable but incorrect technique, with lack of coordination between actuation and inhalation results in decreasing quantities of drug reaching the airways. Spacer devices have been developed to overcome these problems.

Spacer devices. Spacer devices have several theoretical advantages. The aerosol used alone causes much of the drug to be impacted on the posterior pharyngeal wall. The extension spacer allows slowing of the cloud of spray by air resistance and more time for propellant evaporation to occur. This presents smaller particles at a lower velocity with more potential for penetration into the peripheral airways. Studies using labelled Teflon particles have confirmed better deposition in the lungs,[14] but the advantage of distribution to small airways remains unconfirmed. Several devices have been produced commercially, larger ones having the advantage of valves at the mouth end (for example Nebuhaler (Astra), Volumatic (A&H), and Multi-spacer (Medic-Aid) (Fig. 4)), but the smaller ones are much more portable (for example Bricanyl and Pulmicort spacer inhalers (Astra) (Fig. 5)). The decreased need for coordination with valved devices is supported by a study in children showing improved response to terbutaline when using the spacer,[15] but the advantage of a spacer may be minimal when good technique with the aerosol

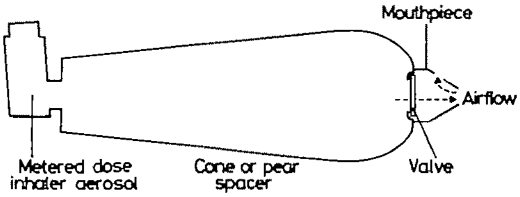

Fig. 4 *Pear or cone valved spacer.*

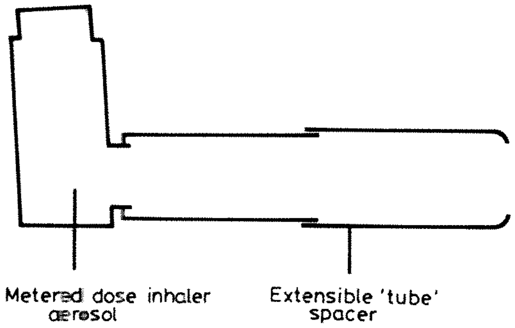

Fig. 5 *Tube spacer.*

exists. During acute exacerbations, when technique deteriorates and bronchoconstriction precludes a big inspiration and a 10 second breath hold, the advantage may be greater.[16,8] A simple device that has been used by some paediatricians has been a standard disposable plastic coffee cup with a hole in the bottom for the aerosol. This can be placed over the face of a young child and used as an extension tube, having the advantage of being cheap and readily available.[17] Its value has been confirmed for bronchodilators, but not yet for cromoglycate or steroids. The large, reservoir, valved spacers may also be of value in these small children, if they can get their lips around the mouthpiece and generate enough flow with tidal breathing to move the valve, as no special manoeuvres or coordination are required. A breath actuated aerosol has been developed (Pulmadil auto (Riker)) but in general it remains unacceptable to children because of the noise and vibration accompanying actuation.

(3) Dry powder inhalers (Fig. 6)

These consist of simple devices which either pierce or split a capsule containing the drug. The drug particles are mixed with a coarser carrier substance (generally lactose) and when the capsule is opened, inhalation through the device creates turbulent flow or spins the capsule causing the aggregates of powder to be broken up and inhaled. This system may not be as efficient as the aerosol, which means that some drugs must be administered in larger doses for an equivalent effect (for example cromoglycate, 2 mg by aerosol and 20 mg by dry powder), but with others it may be as effective (for example salbutamol and beclomethasone dipropionate). The advantage is that minimal coordination is required. Despite this, a steady full inspiration through the device is needed to empty the capsule and this may be difficult when a child is unwell.

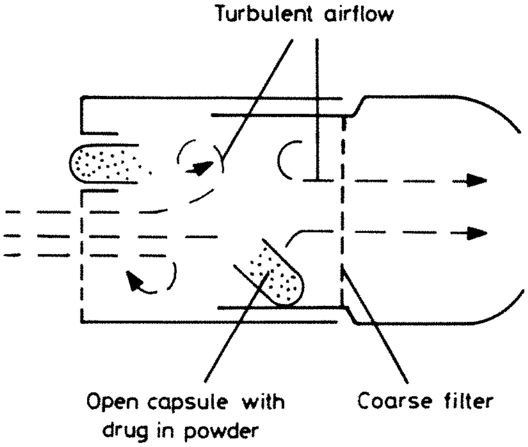

Fig. 6 *Dry powder inhaler.*

There are several groups of drugs useful in the treatment of asthma which are available by the inhaled route.

Bronchodilators. Bronchodilators have been administered by inhaler for more than 50 years,[1] and because of their rapid and easily measured effects have been extensively investigated.[10] Initially, nonselective sympathomimetic agonists such as adrenaline and isoprenaline were used in aerosols as was aminophylline, a methylxanthine. Although effective, they were associated with cardiac side effects which were initially blamed for the increase in asthma deaths during the mid-1960s. This put inhalation treatment under a 'cloud' from which it has not fully emerged. Despite evidence that other factors were implicated in the epidemic of deaths, there was a relation between excessive use of inhalers, although it was not necessarily causal. Today, there are several selective beta$_2$-agonist sympathomimetics available for the treatment of asthma. Studies have shown that administration with intermittent positive pressure breathing has no advantage over nebulisation with tidal breathing. In normal subjects and stable asthmatics, the different inhalation methods of aerosol delivery are equivalent when identical doses of drug are administered.[16] Exercise induced asthma is prevented to a greater extent by inhaled then oral medication.[18] In severe acute asthma, supplementation with systemic sympathomimetics, and sometimes corticosteroids, may be required, although in some cases nebulised medication may be as effective as the same drug administered parenterally. Beta agonists given alone during an acute exacerbation of asthma may cause a fall in oxygen saturation due to vasodilatation, perfusion/ventilation mismatch, and intrapulmonary shunting, although this is less likely with selective beta$_2$-agonists and its clinical importance remains unclear.[19] Beta agonists may have a poor effect in children less than 18 months old.

The anticholinergic agent ipratropium bromide is also an effective bronchodilator, with few atropinic side effects in normal dosage. It is particularly useful in the toddlers when the effects of beta agonists may be limited. A few older children show a better response to it than to the sympathomimetics, and in some the two drugs have an additive effect. It is available in an aerosol and as a nebuliser solution, the latter now being made up with physiologic saline and not with water, the use of which may be associated with bronchoconstriction due to hypotonicity. The methylxanthines are also effective bronchodilators. Although they have been administered by inhalation, the oral or intravenous routes are preferred because these drugs irritate the airways.

Sodium cromoglycate. This is an effective prophylactic agent for asthma. Its mode of action is not completely understood but it is a potent mast cell stabiliser. This property may not be its only or even the most important effect, as other potent mast cell stabilisers, absorbed orally, have not been shown to be as effective in asthma.[20] Cromoglycate is poorly absorbed and is only effective by inhalation. It is available as nebuliser solution, powder aerosol, and an aerosol and the doses which give equivalent effects are 20 mg by nebuliser or powder to 2 mg by aerosol.

Corticosteroids. Corticosteroids are very effective for the treatment of asthma, but given systemically have many serious side effects. Potent topical corticosteroids, which are rapidly metabolised when absorbed, have revolutionised the lives of many moderate to severe asthmatics. They are as effective as systemic steroids in moderate doses without the severe systemic effects. In children, growth retardation when using long term systemic corticosteroids is a particular problem that does not occur with standard doses of inhaled steroids, and as asthma itself can cause growth retardation, some may actually improve their growth rate when started on this therapy.[21]

Oropharyngeal candidiasis is an occasional complication of treatment. It may be related to impaction of the drug on the posterior pharyngeal wall and responds to conventional treatment. If it continues to be a problem it may improve with the use of a spacer device. Dysphonia, which occasionally occurs in adults, is rare in children.

Several inhaled corticosteroids are marketed in this country, with little to chose between them. They are available as aerosols in low and high doses and one as a powder inhaler. Once cromoglycate has failed to control symptoms and inhaled steroids are begun, there is no value in continuing the cromoglycate. High dose steroid aerosols may be advantageous in a few patients who respond poorly to conventional doses and require systemic steroids.[22] Recently, beclomethasone dipropionate has become available as a nebuliser suspension, but in our experience this mode of administration is not as effective as the others. The reasons for this remain to be delineated.

Clinical usage

The advantages of inhalation treatment are as great for children as for adults, but the problems of compliance are greater, particularly in the younger group. Our practice is as follows:

Under 18 months of age. Inhalation therapy is usually only possible using a nebuliser, although an aerosol and cup spacer may occasionally be of use. In an acute episode of wheezing, beta agonists may not be as effective as they later become, perhaps due to immature beta receptors, but they are worth trying, to evaluate the effect. If they are not helpful, ipratropium bromide may give temporary relief of symptoms. For frequent symptoms, regular nebulised cromoglycate may be effective prophylaxis. Unfortunately the equipment is bulky and expensive, and treatment is time consuming. For many children, oral medication may be more acceptable, and they should be given a treatment trial before resorting to nebulisers.

From 18 months to 4 years. Beta 2 agonists become more effective at this age and some use may be made of the valved spacers, but in general, the nebuliser remains the mainstay of inhaled treatment. As soon as the child is able, a mouthpiece is preferable to a face mask to avoid deposition of drug on the face and eyes. Again, oral medication may be more useful in some patients.

From 4 to 8 years. Children of this age can gain increasing skill in using the powder inhalers as minimal coordination is required. This reduces the time required for treatment and improves portability of equipment, as well as enabling the use of inhaled steroids for those resistant to cromoglycate prophylaxis. In some, the powder is thought to be unpleasant, and cromoglycate may cause transient cough (which may be alleviated by pretreatment with a bronchodilator). The valved spacers in conjunction with the aerosol may have an advantage in some patients who prefer this technique but the powder systems allow greater parental control of dosage as the capsules used can be counted—unlike the aerosol which has 200 doses, the fates of which are more difficult to trace.

From about 8 years of age. At this age children gain enough coordination to use the aerosol effectively when trained, allowing them the full range of treatment now available. A spacer attachment may help to deliver a bronchodilator in acute exacerbations but seems to have no advantage for maintenance treatment in those able to use the aerosol efficiently. Again, in those who have difficulty in coordinating, the valved devices may be helpful.

The technique for the aerosol that we teach here is:

(1) Shake the aerosol and remove cap;
(2) Exhale to a comfortable point below functional residual capacity;
(3) Place the aerosol between the lips;
(4) Take a full, steady breath in, to a point near total lung capacity and simultaneously actuate the aerosol;
(5) Hold the breath in for a count of 10 (or as long as possible).

Beginning of inhalation should precede actuation, and we try to coordinate the actuation early during inspiration, although, surprisingly, this is not as important as the slow, steady inhalation and subsequent breath holding.[4] Holding the aerosol in front of an open mouth does not seem to be an advantage.

Common faults in technique that we have encountered are:

(1) Actuation after completion of inhalation;
(2) Actuation during expiration;
(3) Actuation with tongue or teeth blocking the aerosol;
(4) No inhalation (this may occur despite dramatic movement of the head and shoulders);
(5) Inhalation through the nose after actuation into the mouth;
(6) 'Snatched' or rapid inhalation;
(7) Failure to hold breath after inhalation.

These are examples of some of the many errors that must be carefully sought and eliminated. The technique is slightly modified with powder inhalers. The long inhalation needs to be somewhat more powerful (perhaps to create enough turbulent air flow to break up the carrier/drug particles) but coordination is not required and breath holding may not be as important.[25] The aim is to empty the capsule of powder in one, or at most two breaths.

When using a valved spacer, they take several breaths through the device for each actuation, the number depending on the size of the child, with a breath hold at the end of inspiration.

It must be emphasised that in our experience, the main cause of failure of inhalation treatment in children is inadequate technique with the device used or an inappropriate device for that age. A large proportion of children who attend our clinic have previously been prescribed suitable treatment and only require training in when and how to use it. It should be the responsibility of the doctor prescribing an inhalation device to teach its effective use and to check technique at subsequent visits. Although this responsibility may be delegated to another member of staff, a physiotherapist or a practice nurse who has learnt the techniques, the doctor must know the optimal use of the devices prescribed. Aids for teaching technique, placebos and whistle attachments for powder inhalers may help individual patients but there is no substitute for correct tuition. Time spent on this pays dividends in improved control of symptoms.[23] In our department the physiotherapists teach the technique and at the same time train the children in controlled breathing to aid relaxation during exacerbations.

It is also important that the child or parents, or both, know what to do in case of failure of inhalation treatment. In acute exacerbations there may be a relative resistance to beta agonists, difficulty with inhalation technique, and a limitation of inspiratory, as well as expiratory flow,[25] so if poor response to the aerosol or powder system is encountered, a nebuliser, with its relatively higher dose, and easier technique should be tried. This may require calling in the family doctor or visiting the casualty department.

There has been an increase in asthma deaths in New Zealand over the past few years and it has been suggested that this is due to an abuse of nebulisers and bronchodilators available over the counter there.[9] The delay in seeking treatment when using these devices in severe exacerbations may be similar to that thought to have caused the epidemic of deaths associated with the excessive use of aerosols in the 1960s, and so great care must be taken when supplying inhalation devices for home use now. When patients have them at home they should have clear, written instructions on which drugs to use when, and exactly how to make up the solutions for use in the nebuliser. They must also know what to do should that treatment fail to give relief of symptoms and when to seek further help. Therefore our instructions for salbutamol or terbutaline are:

(a) Careful assessment of the effect of treatment must be made, including, if possible, peak flow recording before and after treatment;

(b) Failure to improve means that further medical help must be sought at once;

(c) Improvement which is transient, with deterioration to the previous state or worse within four hours or less needs similar review;

(d) The nebuliser must not be used more frequently than four hourly;

(e) If the child is very ill or deteriorating rapidly, help must be sought at once, as well as giving the bronchodilator.

It is in these situations that further intervention such as systemic bronchodilator or steroid may be needed to prevent deaths,[24] so delay in seeking help must be avoided.

Although we have confined this article to the use of inhalation treatment in asthma, it is used in other conditions, with other drugs. In cystic fibrosis, for example, as well as some use in asthma treatment, the inhaled route has been used for antibiotics and mucolytics.

Future developments include the use of other drugs with potential activity in asthma such as: calcium antagonists, new antihistamines, new xanthines and non-steroidal anti-inflammatory drugs, as well as possible further development of inhalation devices such as breath activated aerosols and multiple dose dry powder inhalers to make them more acceptable to patients.

Nearly 50 years ago, Collison (an English physician) wrote, 'Asthmatics speak of this treatment with enthusiasm compared with the usual forms of therapy . . . The inhalation of adrenaline will stop or avert the attack, and when it is supported by a carefully prescribed course of curative treatment the paroxysms diminish in frequency and the asthmatic habit becomes broken and the tendency to further attacks definitely reduced.'[1] If we change the words 'adrenaline' to 'selective beta 2 agonists', and 'curative' to 'prophylactic', the statement is right up to date. The words 'carefully prescribed' may need underlining as they particularly apply to the training in the use of inhaler devices.

We would like to thank the physiotherapists at the Brompton Hospital for their unfailing support and for the careful training of our patients.

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Archives of Disease in Childhood, 1986, **61**, 95–99

Correspondence

Reversible inhibition of central precocious puberty with a long acting GnRH analogue

Sir,

We were interested to read the recent paper by Ward *et al*[1] about the effect of the GnRH analogue (6-D-Ser) GnRH(Buserelin) on gonadotrophin pulsatility. This report raises the question of analysis of pulsatile hormone secretion, which has only recently come to the fore in paediatric practice. Because studies of this type will be increasingly performed, we wish to draw attention to what can and, perhaps more importantly, what cannot be learned from different methods of sampling.

It is apparent that the biological effect of both gonadotrophins[2] and growth hormone[3] are related to the pulsatile pattern of their secretion and not to mean blood concentrations. There is no consensus on the optimum method to identify gonadotrophin pulses in serum,[4] although the method most commonly used is to withdraw blood during a 5–10 second period and repeat this procedure at intervals. The sampling interval needs to be chosen to reflect the approximate frequency of the natural hormone pulsatility and the biological half life of the hormone. For both gonadotrophins and growth hormone, the maximum time interval should not be greater than 15–20 minutes. The more frequent the sampling interval, the more pulses are detected.[4] The method that Ward *et al* used was to withdraw blood continuously over 15 minutes and to measure the gonadotrophin concentration in the pooled sample. This method is not capable of revealing the frequency and amplitude of gonadotrophin pulses in serum unless very short (5 minutes or less) sampling intervals are employed.

Further ambiguity has been caused in Ward's study by the use of sampling periods that varied between four and three quarters and five and three quarters hours. These are short compared with the known frequency of gonadotrophin pulses in puberty, which occur approximately every two hours.[5] A more appropriate sampling period would be longer than eight hours.

The data presented by Ward *et al* provide information about mean serum gonadotrophin concentrations at night, but it is pulsatile gonadotrophin secretion that is the stimulus for gonadal maturation. As the authors have not assessed gonadotrophin pulsatility, their claims about reversibility of the effect of (6-D-Ser)GnRH could be premature.

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Rectal examination and acute appendicitis

Sir,

The short report on 'Rectal examination and acute appendicitis'[1] records the findings of two paediatric surgeons but fails to make a useful contribution for other clinicians managing children with acute abdominal pain. I am concerned that paediatricians, who are often reticent about performing rectal examinations, will quote this study as a reason for omitting this part of the clinical examination. The management of acute abdominal pain in children is not straightforward and 'the man on the spot' needs unequivocal guidelines rather than the contemplation of the fact that his colleagues can diagnose acute appendicitis in over 90% of cases without rectal examination. This report, which works back from the histology of the removed appendix to the clinical findings, is of no help to the surgeon at the bedside.

The third conclusion that 'the rectal examination is sometimes useful when the diagnosis is uncertain' is too vague for the trainee duty surgeon. The correct emphasis appears in the middle of the discussion where the rectal examination is described as 'essential in those with acute abdominal symptoms, but with inconclusive or no abdominal signs'. This imperative should be given more prominence in the presentation and not omitted from the summary and conclusions.

A careful history and a thorough examination of the patient are essential,[2] and the teaching of Hamilton Bailey is ignored at our patients' peril. Perhaps your journal will publish a paper which makes a positive contribution to the management of the child with acute abdominal pain and thus encourages safe clinical standards for 100% of our patients rather than 90%.

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Insufficient early weight gain in preterm babies and influence on weight at 12 months

Sir,

In an interesting though difficult paper Davies and Kennedy[1] report that there was no influence of insufficient early weight gain in preterm babies on weight at 12 months.

I would like to comment on their introductory remarks that anxieties about poor early weight gain were 'based largely and often uncritically on studies in laboratory animals', citing a (wrongly dated) 19 year old paper by Winick and Noble that has now lost its currency,[2] a classic paper of Widdowson and McCance, and an old one of our own.

It is true that paediatricians' extrapolations from other animals to man are often uncritical, to the point that they may be rejected altogether except where they seem to bolster emotional belief,[3] and this example is no exception. At the same time such comparisons can be very useful and should not be dismissed until they have been properly made. At the very least they must take account of the different time scales of growth between species, the different timing of birth in relation to developmental stages, and, especially, comparable stages of growth must be compared before the self evident conclusion is pronounced that animals are 'of course' not always like man.

In the present case growth restriction between birth and three weeks of age in the rat clearly results in a permanent resetting of the growth trajectory downwards, with ultimate stunting in adulthood, and in certain permanent alterations of brain anatomy and function. The comparable period in man is much longer, from about the beginning of the first trimester of gestation until about the second birthday. Whether or not man has a similar vulnerable period to that in rats awaits a demonstration of the *long term* consequences of growth restriction lasting for *a major part at least of this very long period in humans*, such restriction being to a comparable degree, so that by the age of 2 the child is not much more than half its ordained size, the outcome being assessed not earlier than the late teens. Of course, it is much easier to produce these conditions in experimental animals, but that is the whole point of using them. Children do exist, especially in underprivileged communities, whose early growth experience comes reasonably close to the model suggested by Widdowson and McCance in the rat, and there is reason to believe that in them a *critical* extrapolation bears fruit, the people in such communities being generally stunted. That the reason for their smallness is by no means wholly genetic is evident from their children's response to the arrival of better environmental conditions, when they are seen to outstrip the growth attainments of their parents, often dramatically.

I hope that the strictures of Davies and Kennedy about extrapolating from animals to man will be heeded, not least by themselves!

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Professor Davies and Dr Kennedy comment:

We are grateful to Professor Dobbing for his comments. These serve to strengthen even further our already held conviction of the need to consider and analyse very carefully any extrapolations that might be made from animals to man in regard to effects of nutrition on early growth. We will be dutiful in applying these strictures to ourselves!

Impact of neonatal care—South West Thames region (less than 1000 grams)

Sir,

Thompson and Khot[1] have reported on the Brighton (South East Thames) experience on the reduction of mortality with the introduction of respiratory support. Not only does local mortality improve but so do expectations, and this is not just confined to the centres providing full neonatal intensive care with respiratory support. In the next door South West Thames region intensive care began probably with the opening of a new unit at St George's in 1980. In the five years 1980–84 inclusive there has been a steady improvement in mortality figures both at St George's and generally in the region. This has been accompanied by a regional increase in expectations. This is illustrated by the Table.

In 1980, 53 infants delivered with a birthweight less than 1000 g were resuscitated in the region, 13 (24%) at St George's Hospital. Since then there has been a steady increase, so that in 1984 there were 72 infants of this weight resuscitated, 28 (39%) at St George's. In 1980 only eight infants <1000 g in the region survived to go home, four (50%) from St George's—that is, only 15% of those resuscitated. This had increased to 39 infants in 1984, of whom 18 (46%) were delivered at St George's. Thus the overall regional survival for babies of this weight group has increased to 54%. Not only are more infants of this extremely low birthweight being resuscitated, but they are

Table *South West Thames: No (%) of babies of birthweight <1000 g resuscitated and surviving to go home*

	1980	*1981*	*1982*	*1983*	*1984*
Resuscitated:					
St George's Hospital	13	18	18	27	28
Rest of SW Thames region	40	39	42	37	44
Total	53	57	60	64	72
Surviving to go home:					
St George's Hospital	4 (31)	10 (56)	9 (50)	16 (59)	18 (64)
Rest of SW Thames Region	4 (10)	10 (26)	17 (40)	11 (30)	21 (48)
Total	8 (15)	20 (35)	26 (43)	27 (42)	39 (54)

being effectively resuscitated and generally around the region are being managed so that they can go home. The greater expectations have implications for the provision of care. Intelligent anticipation by regional obstetricians with in utero referral is now commonplace, and baby units that are not staffed to practise even short term care provide effective resuscitation, so that the percentage of infants dying before transfer to an intensive care unit has fallen from 40% in 1980 to 19% in 1984.

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Food related asthma: a difference between two ethnic groups

Sir,

I read the article by N M Wilson[1] with interest. I was not surprised by the findings and feel I must express some reservation regarding its conclusions.

As a severely atopic child growing up in South India I can remember well my parents' admonitions relating to iced and fizzy drinks, fried foods, nuts, and chocolate. A deep sense of guilt, and a heavy wheeze, often accompanied my return home from children's parties. In the family inquest that usually ensued the atmosphere of dark suspicion and recrimination did little to alleviate bronchospasm. A school mate suffering from recurrent cystitis had similar food restrictions imposed (ice 'brought a chill to the kidneys').

Auto suggestion certainly played a major role in my reaction to foods. When, at the age of 21, I made the decision to remove milk and eggs from my diet a complete and permanent resolution of eczema resulted within weeks. Asthma that had been controlled for eight years only by the use of continuous systemic steroids regressed to four or five attacks a year. These are now triggered off by common antigen exposure—that is, house dust, pollens, and heavy exercise.

There are widespread food taboos on the subcontinent. The above mentioned foods are often incriminated in many relapsing ailments—for example, diarrhoea and migraine. Conversely, foods considered beneficial, like milk and eggs, are rarely, if ever, considered for indictment.

I therefore find it difficult to accept the conclusion that Asian asthmatic children have food sensitivities that are in any way excessive or peculiar. A control study of Asian children with non-asthmatic chronic disorders might be of value. It would also be interesting to know what proportion of the children studied derived from homes where first or second generation traditional influences still apply.

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Dr Wilson comments:

The implication of Dr de San Lazaro's letter is that the ethnic difference found in the survey could merely be the spurious result of cultural taboo and that any experience of food related asthma in the Asian children was due to suggestion. She provides no evidence, however, that her symptoms as a child, after ingestion of certain incriminated foods, were in fact psychogenically determined rather than a genuine response to the ingested substances. In contrast, the claim that ice, fizzy drinks, and fried foods can precipitate asthma in Asian subjects was based on the results of controlled challenge tests.[1-3] I think it highly unlikely that these positive responses were due to suggestion even when the tests were performed single blind. For example, ice but not placebo induced a significant increase in bronchial responsiveness that was greater at 90 than 30 minutes after ingestion, without a change in resting lung function.[1] Because of the way the tests were conducted the subjects were unaware whether a positive response had occurred or not. Suggestion can undoubtedly induce bronchoconstriction, but an increase in bronchial responsiveness due to psychogenic factors has not been reported. Admittedly, one cannot be sure that every child giving a positive answer in the survey had experienced such an effect nor that all those with negative answers had not. However, positive histories were confirmed in almost all of the Asian children challenged with ice,[2] cola drinks,[3] and fried foods.[1] On the other hand, asthma in the older child due to milk or egg intolerance, in the experience of myself and others using diagnostic elimination diets, is uncommon. It is not suggested that the incriminated substances are the cause of asthma in Asian children but rather that they act as an asthmogenic stimulus, as do exercise and smoke in asthmatics in general.

A control study of Asian children with non-asthmatic chronic disorders might be interesting but irrelevant. The fact that other disorders such as cystitis may be erroneously attributed to the same substances does not invalidate the asthmatic response that has been shown.

All the children were born in this country, but cultural influences may still prevail. I maintain that this particular folklore is based on fact.

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Problems facing women who seek a career in paediatrics

Sir,

As the pair of successfully matched job sharing doctors mentioned in Dr C Rees's annotation[1] we have encountered many of the difficulties she lists. We would still like to emphasise, however, the hopeful side of the future for women in paediatrics.

In September 1984 the proportion of female consultants in post was 17%; between 1978 and 1983, 20% of new consultants and senior registrars were women.[2] Around 1968, when these new consultants finished medical school, the proportion of women graduating was 24%.[3] Women are, therefore, relatively well represented in paediatrics. We are certainly more fortunate than those in other acute specialties; for the same period, only 4% of new consultants and 7% of new senior registrars in general medicine were women.

As the proportion of female graduates entering paediatrics increases the requirements for part time work will rise. There are also men who would appreciate a period of part time work, either for writing up research or seeing more of their young families. Is it not time that the British Paediatric Association set up its own job share register?

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Dr Chambers, secretary of the British Paediatric Association, comments:

This is now being done: enquiries to Dr Rosamond Jones, 15 Fairfield Lane, Farnham Royal, Bucks.

Risk and pertussis vaccine

Sir,

During the current epidemic of whooping cough many parents are reconsidering pertussis immunisation for their infants, and paediatricians are being asked about risks and benefits. The National Childhood Encephalopathy Study (NCES)[1, 2] conducted with the close cooperation of paediatricians in 1976–79 was designed to help answer their questions, and we are often asked about the interpretation of our results.

The NCES was a case control study in children admitted to hospital with acute neurological problems, in which we compared the histories of immunisation shortly before onset in cases with similar histories in controls. The first report included only 1000 of 1182 children notified to the study,[1] though inclusion of the remaining children did not materially alter our findings.[3] Our analysis included *all* children without regard to any alternative explanation apart from pertussis immunisation. This epidemiologically essential approach is not always understood and has led some to believe that the study shows the risks of pertussis vaccine to be greater than they are. It has also been suggested that our estimate of risk is too low due to bias in case reporting, but, as explained in our report, this is unlikely to have materially affected the results.

We reported two types of risk estimate:

(a) Relative risk. There was a small but significant excess risk of children having had DTP vaccine in the seven days before onset of a serious neurological disorder. Most of this excess was in the first 72 hours. Fortunately, most recovered quickly and were apparently normal when followed up at least a year later. No recognisable 'post pertussis immunisation syndrome' was found.

(b) Attributable risk. The attributable risk of these events was about one in 140 000, but the central estimate of risk of death or permanent damage comes to around one in a third of a million doses of DTP vaccine in children who were assumed (but not proved) to have been previously fit neurologically. We stress that this figure must be interpreted with caution because the 95% confidence limits are very wide and it assumes all relevant cases were notified. In fact it is based on *only seven* children found in a three year period. Of these seven, two died, one with Reye's syndrome and one with an overwhelming viral infection. One child with major defects had Coxsackie B5 virus isolated from the CSF, which could have been the cause of illness. This leaves four children, only one of whom was severely handicapped when last seen, with no alternative explanation for their illness. The real cause of the handicap in these children remains in question—was it a reaction to vaccine or did they have some other undiagnosed problem? It must be remembered that pertussis immunisation is given at the very age when children are most likely to manifest serious neurological disorders. In the circumstances it is clearly unwise to attribute a causal connection in individual cases.

Our view remains, therefore, that the risk of death or brain damage attributable to pertussis vaccine, if it occurs at all, is a very rare event and far less than the risk of death or damage due to whooping cough.[3]

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Inguinal hernias are common in preterm infants

Sir,

We read the paper by Boocock and Todd with great interest;[1] although the higher incidence of hernias in preterm children is generally accepted, accurate figures are difficult to obtain.

The risk percentages stated in the above mentioned article, however, are based on retrospective analysis of cases, surgically treated during the first six months of life, and, therefore, might still be an underestimation.

To clarify this issue we analysed the data on inguinal hernias that have been collected in the course of a nationwide project in The Netherlands, concerning liveborn preterm (<32 weeks) and/or very low birthweight (<1500 g) infants.[2] The study included 1338 liveborn infants (mean gestational age 30·3 weeks, 1095 infants <1500 g, 52% boys). Preliminary results show that of the 978 surviving infants, 94 infants had inguinal hernias before the corrected age of 6 months; 73 (78%) of those have had a herniotomy during that period. In our material a predominance of boys was found as well, whereas unilateral hernias outnumbered bilateral ones both in the total number of hernias and in the surgically treated ones (Table).

Table *Number of infants with inguinal hernia under the corrected age of 6 months*

	Total			*Surgically treated*		
Unilateral:	61			45		
Boys		42			36	
Girls			19			9
Bilateral:	33			28		
Boys		31			26	
Girls			2			2
Total	94 (7%)	73 (10%)	21 (3%)	73 (5%)	62 (9%)	11 (2%)

For calculation of the incidences, we used as a denominator the total number of liveborn infants in a category and not the number of surviving infants. In agreement with Boocock and Todd the incidence is thus independent from the neonatal and postneonatal mortality. Otherwise, differences in mortality may cause considerable differences in incidence of later morbidity such as hernias, resulting in incomparability.

In our study the high incidence of inguinal hernia in preterm and very low birthweight infants is confirmed; even if the cases that were not yet surgically treated are included, however, the incidence is clearly lower than in Boocock and Todd's study.

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rchives of Disease in Childhood, 1986, 61, 100-101

Book reviews

e Health and Social Needs of Physically ndicapped Young Adults: Are They ing Met by the Statutory Services? De- opmental Medicine and Child Neurol- y Supplement No 50. By A Thomas, Bax, K Coombes, E Goldson, D Smyth, Whitmore. Pp 20: £2·00 paperback. astics International/Blackwell Scientific, 35.

the foreword to this slimmest of oklets states, the handicapped child has at emotional appeal for fund raising; the ılt, even the young adult, does not. The ection of the young handicapped adult y be because 'in some way they reveal to who we are'. However such rejection ses, its results are only too evident in a ge and complex advanced society such as ıt of the United Kingdom. This summary studies reveals these defects in provision h striking clarity and excellent docu- ntation.

t concerns the services and resources ilable to physically handicapped young ople from the age of 16, when they leave shelter of school and the comprehen- e care of paediatricians. As one would ect, much of the research quoted re- ed to numerically dominant groups, to ebral palsy, spina bifida, and muscular trophy.

The majority of such young adults lost ntact with health services and did not ow how to find the speech therapists, ysiotherapists, and others who were portant to them; there is much evidence t their needs were not being met. despread dispersal of these young ople presents a problem, not least in cumenting their use of and need for hopaedic intervention.

The three main categories of difficulties à vis housing adaptations and the ovision and repair of aids and equipment l come as no surprise to those in the ld: no provision, poor assessment and ulting unsatisfactory provision—all were ominent.

t seems that incontinence is often poorly lt with, insufficiently investigated, and scribed few aids. Dental health, too, eds attention; sex counselling is a press- need—it is often inadequate and largely ffective, and factual sexual knowledge y be poor. These young people also have many other anxieties, related to marriage and the production of children, to employment, and to housing.

This booklet is not just a catalogue of a sorry state of affairs. It is a valuable reference source that is well written and easy to read, but it also proposes some solutions to the young people's lack of support, in particular the formation of a Handicapped Adult Team. Alternatively, in some situations a well placed and dynamic individual professional may achieve much. Whatever solution is found, this survey will probably provide much of the ammunition necessary to improve the lot of older children whose future already fills their paediatricians with alarm.

ANNE CHAMBERLAIN

Pediatric Thyroidology. (Pediatric and Adolescent Endocrinology). Edited by F Delange, D A Fisher, P Malraux. Pp 412: $117·25 hardback. S Karger AG, 1985.

This is a multi-author volume, the 14th title in the series 'Pediatric and Adolescent Endocrinology' under the general editorship of Dr Zvi Laron. It contains 26 chapters grouped into 13 sections, which cover most aspects of the development, function, and malfunction of the thyroid axis in the fetus, infant, and child.

The ugly title and the dull brown cover (bearing one of those flow diagrams in which thyroid hormones scatter in all directions) suggest that this is a down to earth work of science, and so indeed it proves. Each chapter is a concise topic review. Although few are a pleasure to read, most are thoroughly workmanlike and packed with well organised and well referenced facts that are admirably up to date. The chapters on development and function are of particular interest, reflecting the rapid recent advances in knowledge of these areas, but those on the clinical aspects of thyroid disease in childhood cover rather superficially much well trodden ground. The book is well produced but expensive.

This is not a reference book on thyroid disease for the general paediatrician, but as a synopsis of current understanding of the pathophysiology of thyroid disease in c hood it will prove extremely valuabl

NICK BA

Practical Pediatric Therapy. Edited by Eichenwald, J Ströder. Pp 1169: DM hardback. VCH Publishers, 1985.

The authors set out to compile a boo paediatric therapy 'based on the k ledge and experience of North Am and Europe'. Each section is written jo by an American and German author, there are 97 contributors in all. De this, the style throughout is uniform clear. The 35 chapters include neon ogy, nutrition, behavioural disor abuse and neglect, allergy, immunisati antimicrobials, infections, oncology, accidents and poisoning, as well as system disorders and surgical conditi

There is usually a brief outline of aetiology and features of the disorder, the emphasis is on treatment. In gen this is up to date and detailed. Ques able practices are criticised. Dosages given in mg/kg or M^2, but SI units are employed.

I enjoyed the comprehensive neon ogy chapter (64 pages) outlining inte and special care. There are omissi however—for instance, there is no me of anaemia of prematurity or folate quirement. The account of the princip antimicrobial treatment is excellent, cluding data on the new penicillins cephalosporins. Sound guidance is give immunisations, including the current v on timing and contraindications. surgical chapters give a useful, account of the management of com disorders, and the orthopaedic sectio illustrated.

In places, the effort to be compl comprehensive causes cluttering with s ments of the obvious. For instance, section on neonatal resuscitation states the resuscitation bag should not leak the operator should be familiar with equipment. Unfortunately, the inde muddled and often quotes the wrong number.

This fairly expensive book is packed with useful information and would be good for reference in the side room and possibly for postgraduate students.

C A S GALLOWAY

Clinical Reviews in Pediatric Infectious Disease. Edited by J D Nelson, G H McCracken Jr. Pp 315: £44·00 hardback. C V Mosby (Blackwell Scientific), 1985.

The editorial intention is to offer a bridge between the standard textbook and the journal literature with a collection of revised essays from the early issues of *Pediatric Infectious Disease*. There are informative sections on the prevention of infection and on infections in the compromised host, with particular emphasis on the child with cancer, before discussion of selected antimicrobial agents and selected diseases. The book concludes with a brief review of rapid laboratory diagnostic aids to infection.

The prophylactic use of both antibiotics and vaccines is discussed, with clear statements of the present state of knowledge and practical clinical advice, relevant to the general paediatricians as well as to the infectious disease specialist. A sense of proportion is maintained, with discussion ranging from the benefits of careful handwashing to the possibilities of future advance in the field of bacterial vaccines.

The review of antimicrobial agents includes a useful guide through the confusion of the third generation cephalosporins, a balanced comparison of the anti-pseudomonas penicillins, and an excellent directive on how best to use chloramphenicol.

Those articles reviewing selected diseases and conditions cover a wide and disparate range and will not be of interest to all. The treatment of problems such as urinary tract infection and diarrhoea vie for space with discussion of tularaemia and botulism in infancy. The closing review does not adequately explain the laboratory tests discussed.

Important subjects are covered in greater depth than in the average textbook, and there is much informative reading. I doubt, however, if all the articles will achieve the editors' aim of being a standard reference work for several years.

S P CONWAY

Iatrogenic Disorders of the Fetus, Infant and Child. Vol 1. Radiology of Iatrogenic Disorders Series. Edited by E G Kassner. Pp 401: DM440 hardback. Springer-Verlag, 1985.

In a series under the title 'Radiology of Iatrogenic Disorders' it says something for paediatrics that it has been necessary to present two volumes. This, the first volume, covers complications of investigative procedures; diagnostic radiology angiography, and invasive neurodiagnosti studies, followed by iatrogenic disorders i the fetus, in the perinatal period, and o neonatal intensive care. Drugs, nutrition immunisations, and the treatment of childhood cancer complete the volume.

The book is liberally illustrated, and th reproduction of radiographs is excellent Some sections have the same fascinatio that the annual reports of the medica defence societies have, but this is far mor than just a catalogue of disasters. There is detailed explanation of the radiographi features of every problem, which will be o special interest to radiologists. Each chapter presents a detailed historical an epidemiological review of conditions requiring investigation and management Some horrifying examples are presente that make one feel that it should b compulsory reading not only for paediatricians but for cardiologists and surgeons a well. Each chapter is concluded by a full reference list that is reason enough for every department to purchase a copy, though for this purpose if the references were compiled in alphabetical order they would be much easier to refer to.

This is a most comprehensive description of paediatric iatrogenic disorders, but at over £100 it may be confined to library shelves to be referred to from time to time.

ANDREW WILKINSON

Archives of Disease in Childhood, 1986, **61**, 102

Meetings in 1986

Neonatal Society
20 February, London
Further details: Dr N R C Roberton, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ

4th International Child Neurology Congress of the International Child Neurology Association
16–21 March, Israel
Further details: Congress Secretariat—ICNA, P O Box 29313, Tel Aviv 61292, Jerusalem, Israel

Paediatric Research Society
21–22 March, Glasgow
Further details: Dr G S Clayden, Department of Paediatrics, St Thomas's Hospital, London SE1 7EH

British Society of Allergy and Clinical Immunology
4 April, London
Further details: Dr J O Warner, Secretary, BSACI, Brompton Hospital, Fulham Road, London SW3 6HP

British Paediatric Association—58th Annual Meeting
15–19 April, York
Further details: British Paediatric Association, 23 Queen Square, London WC1N 3AZ

Neonatal Society/Swedish Neonatal Society (provisional)
22–25 May, Gothenburg
Further details: Dr N R C Roberton

European Society for Paediatric Gastroenterology and Nutrition (ESPGAN)
25–27 June, Edinburgh
Further details: Professor A S McNeish, Institute of Child Health, Francis Road, Birmingham B16 8ET

1st Scientific Meeting of the British Society for Paediatric Dermatology
9 July, Sheffield
Further details: Dr J L Harper, Westminster Hospital, Horseferry Road, London SW1

5th International Congress of Developmental Disabilities
18–19 July, Osaka, Japan
Further details: Professor H Yabuuchi, Department of Paediatrics, Osaka University Medical School, Fukushima-ku, Osaka, Japan 553

European Society for Paediatric Endocrinology—25th Annual Meeting
31 August–3 September, Zurich, Switzerland
Further details: Professor A Aynsley-Green, Department of Child Health, Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH

European Society for Clinical Respiratory Physiology/European Society of Pulmonology
3–6 September, Paris
Further details: Dr P Helms, Respiratory Unit, Hospital for Sick Children, Great Ormond Street, London WC1N 3JH

European Society for Paediatric Research
8–10 September, Groningen, The Netherlands
Further details: Professor J Fernandez, Department of Paediatrics, University Hospital, Oostersingel 59, ML 9713 EZ Groningen, The Netherlands

Paediatric Research Society
19–20 September, Nottingham
Further details: Dr G S Clayden

British Association of Perinatal Paediatrics (jointly with Royal College of Obstetricians and Gynaecologists)
29–31 October, Leicester
Further details: Dr N R C Roberton, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ

British Society of Allergy and Clinical Immunology
31 October, London (London to be confirmed)
Further details: Dr J O Warner

Neonatal Society
6 November, London
Further details: Dr N R C Roberton

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Instructions to authors

Papers for publication should be sent to the Editors, *Archives of Disease in Childhood,* BMA House, Tavistock Square, London WC1H 9JR.

Submission of a paper will be held to imply that it contains original work not being offered elsewhere or published previously.

Manuscripts should be prepared in accordance with the Vancouver style.[1]

The editors retain the right to shorten the article or make changes to conform with style and to improve clarity.

For guidance on ethical aspects refer to the editorial in this journal.[2]

All authors *must* sign the letter of submission.

Original articles

These should usually conform to the conventional structure of summary, introduction, methods, results, discussion, and references. The title should occupy no more than two lines of the title page (8 to 10 words) and should not contain the words 'child', 'children', or 'childhood' (already implicit in the title of the journal). The summary should be no longer than 150 words and should set out what was done and the main findings and their implications.

Short reports

Short papers, brief laboratory observations, and preliminary communications should be submitted for this section (single case reports will usually be considered in this form only). Length must not exceed two printed pages of text. In general this will be less than 900 words, including a summary of less than 50 words, one or two small tables *or* illustrations and up to 6 references. An abbreviated title of no more than 38 characters is required for the title page. A report of a negative result trial, based on a reasonable hypothesis, is more likely to gain acceptance if submitted as a *very* short report of less than 500 words.

Annotations

Annotations are commissioned by the editors who welcome suggestions for topics or authors.

Letters

Letters should normally be no more than 300 words, have no more than three references, and be signed by all authors. They should be prepared in a similar way to other manuscripts. Preference is given to those that take up points made in contributions published in the *Archives* but those that discuss current topics or present original observation may be acceptable.

Manuscripts, tables, and illustrations

Manuscripts should be typed double spaced on one side of the paper with a 5 cm margin at the top left hand side of the sheet. The pages must be numbered. Authors should keep one copy of their manuscript and submit two copies; if the paper is rejected it will not be returned unless this is requested at the time of submission. Three copies of revised versions of manuscripts should be submitted. The authors should include their family names and initials and the place where the work was done; their number should be kept to a minimum and should include only those who have made a contribution to the research: justification should be made for more than five authors. Acknowledgements should be limited to workers whose courtesy or assistance has extended beyond their paid work, and to supporting organisations. The name and address of the corresponding author and whether or not reprints will be available, to be given at the end of the paper.

Drugs should be given their approved, not proprietary names, and the source of any new or experimental preparations should be given. Abbreviations should not be used. Scientific measurements should be given in SI units: conversion factors to traditional units should also be supplied. Blood pressure, however, should be expressed in mmHg and haemoglobin in g/l.

Any statistical method used should be detailed in the methods section of the paper and any not in common use should be either described in detail or supported by references. Previously published procedures and techniques need only a reference to the original. Tables and illustrations should be submitted separately from the text of the paper, and legends to illustrations should also be typed on a separate sheet. Tables should be simple and should not duplicate information in the text of the article, they should be numbered and be comprehensible to the reader without the text.

Illustrations should be used only when data cannot be expressed clearly in any other way. When graphs or histograms are submitted the numerical data on which they are based should be supplied. Line drawings should be in Indian ink on heavy white paper or card, with any labelling on a separate sheet, they may also be presented as photographic prints. Other illustrations should usually be prints—not negatives, transparencies, or *x* ray films; they should be no larger than 30 × 21 cm (A4) and be trimmed to remove all redundant areas; the top should be marked on the back. Staining techniques of photomicrographs should be stated. Either an internal scale marker should be included on the photomicrograph or the final print magnification of the photograph itself should be given. Again, any labelling should be on copies, not on the prints. Patients shown in photographs should have their identity concealed or should give their written consent to publication. If any tables or illustrations submitted have been published elsewhere written consent to republication should be obtained by the author from the copyright holder (usually the publisher) and the authors.[1]

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Most articles do not require more than 20 references and many need substantially less. References should be numbered in the order in which they appear in the text. At the end of the article the full list of references should give the names and initials of all authors (unless there are more than six, when only the first three should be given, followed by *et al*). The authors' names are followed by the title of the article, the title of the journal abbreviated according to the style of *Index Medicus* (see the January issue of *Index Medicus*); the year of publication, the volume number; and the first and last page numbers. Titles of books should be followed by place of publication, publisher, and year.

1 Barson AJ, Tasker M, Lieberman BA, Hillier VF. Impact of improved perinatal care on the causes of death. *Arch Dis Child* 1984;**59:** 199–206.
2 Dowling S. *Health for a change*. London: Child Poverty Action Group, 1983.

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References

[1] International Committee of Medical Journal Editors, Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1982;**284:**1766–70.
[2] Anonymous. Research involving children—ethics, the law, and the climate of opinion. [Editorial]. *Arch Dis Child* 1978;**53:** 441–2.

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Monatsschrift Kinderheilkunde

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Oktober 1985

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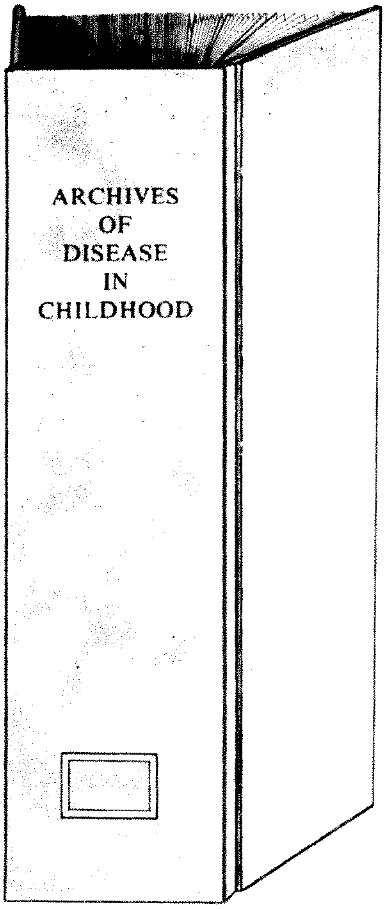

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Mar 17–21	CHILD PSYCHIATRY	Prof P J Graham

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	GENETIC ENGINEERING	Dr M Pembrey
	DIAGNOSIS OF DYSMORPHIC SYNDROMES	Dr M Baraitser
	PAEDIATRIC NEUROLOGY	Dr E Brett
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sed with anticonvulsants which induce
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The Journal of the British Paediatric Association

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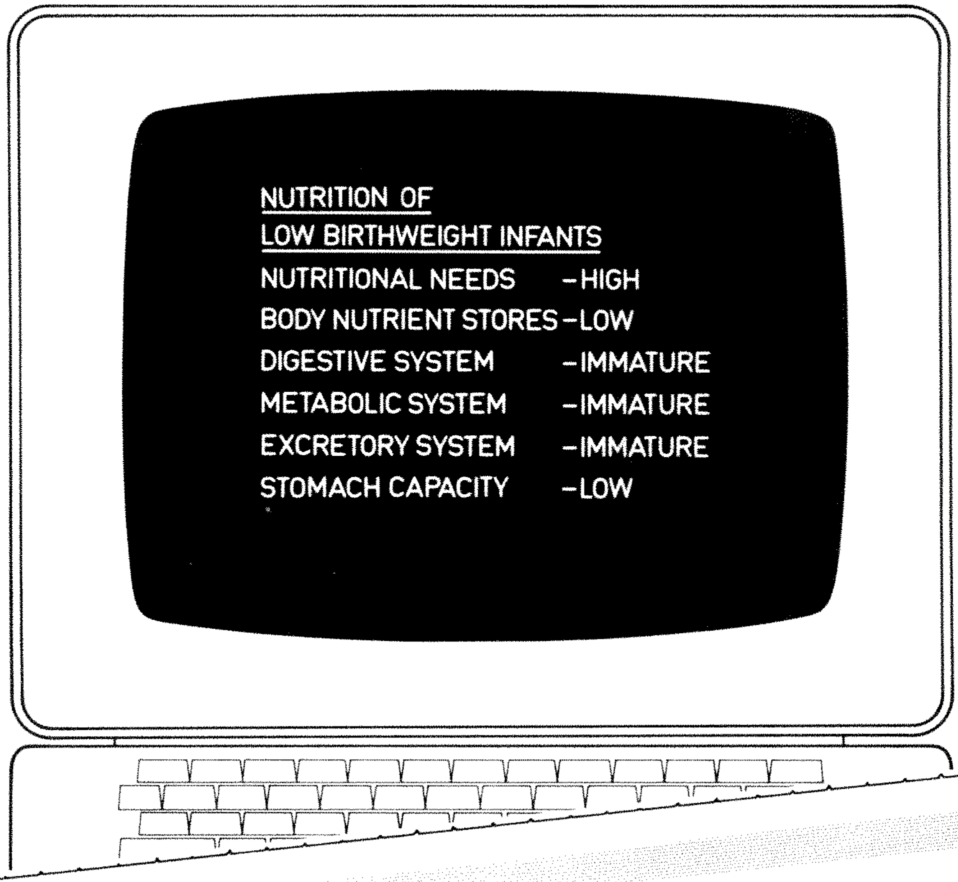

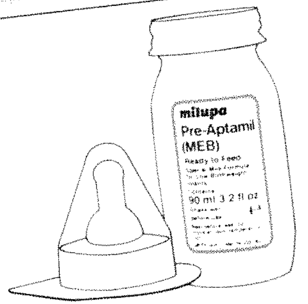

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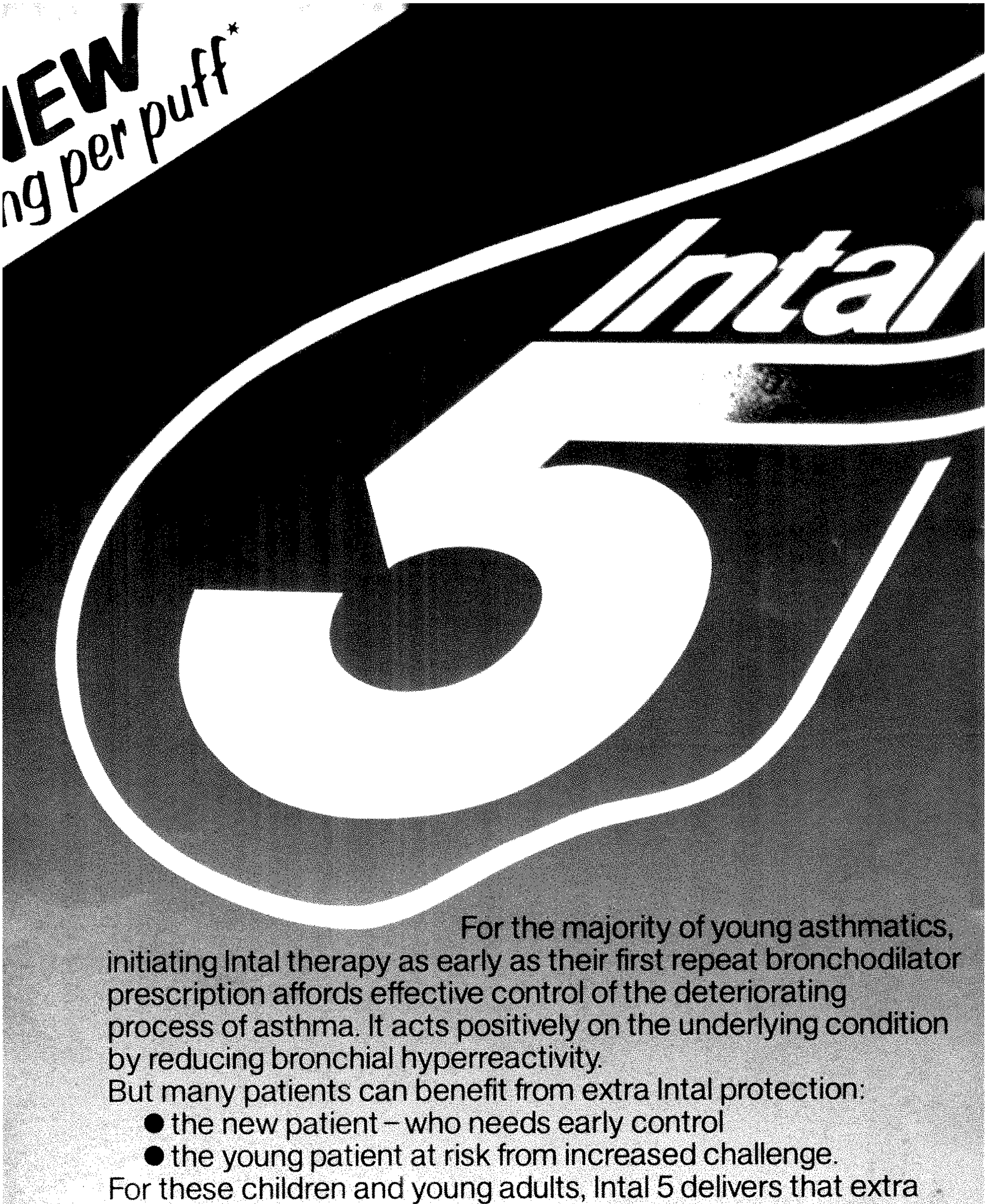

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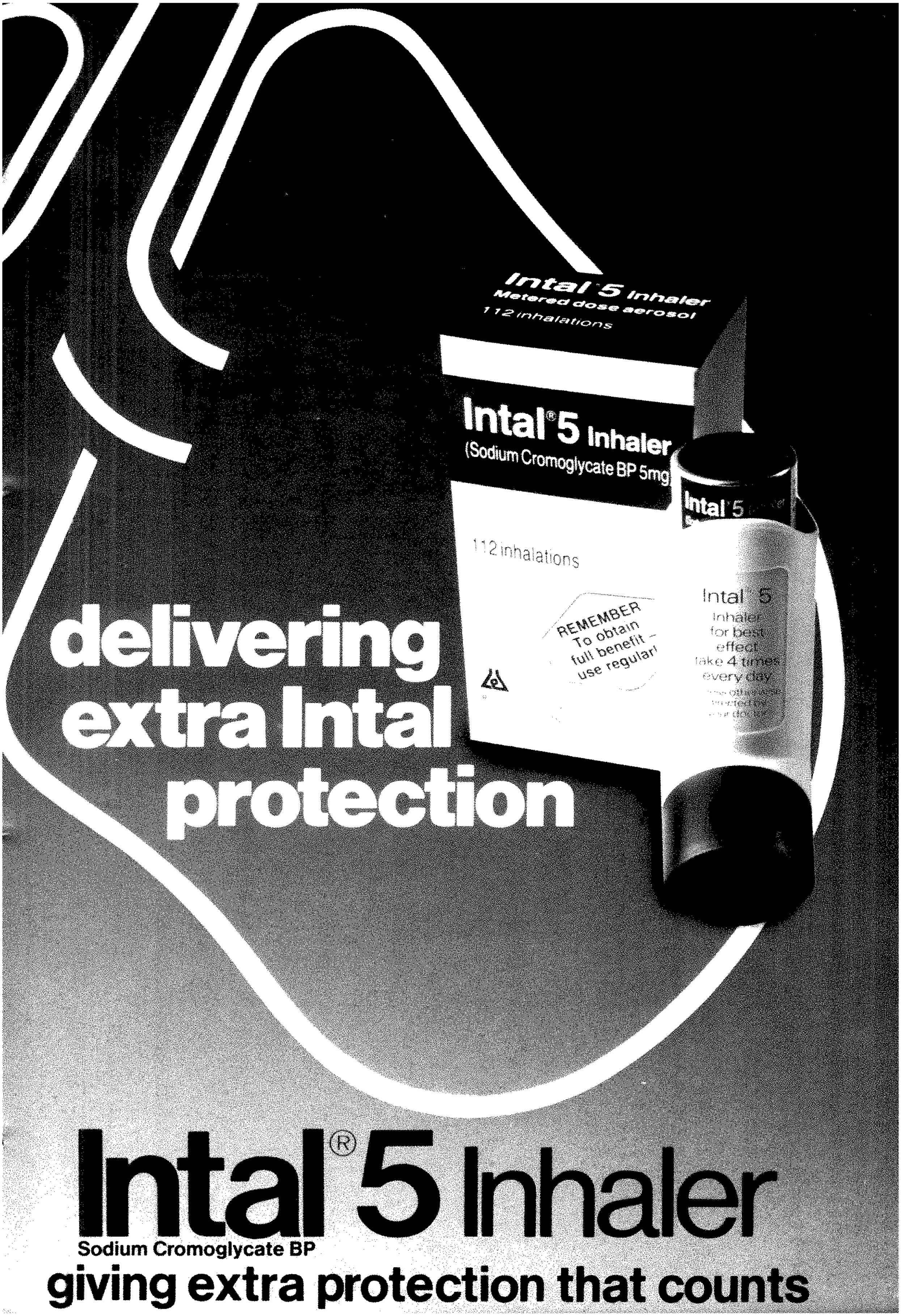

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1. Johnson I.S., Diabetes Care 1982, Vol. 5, Suppl. 2, 4-12. 2. Fineberg, S.E. et al, Diabetologia 1983, **25**, (6) 465-469.

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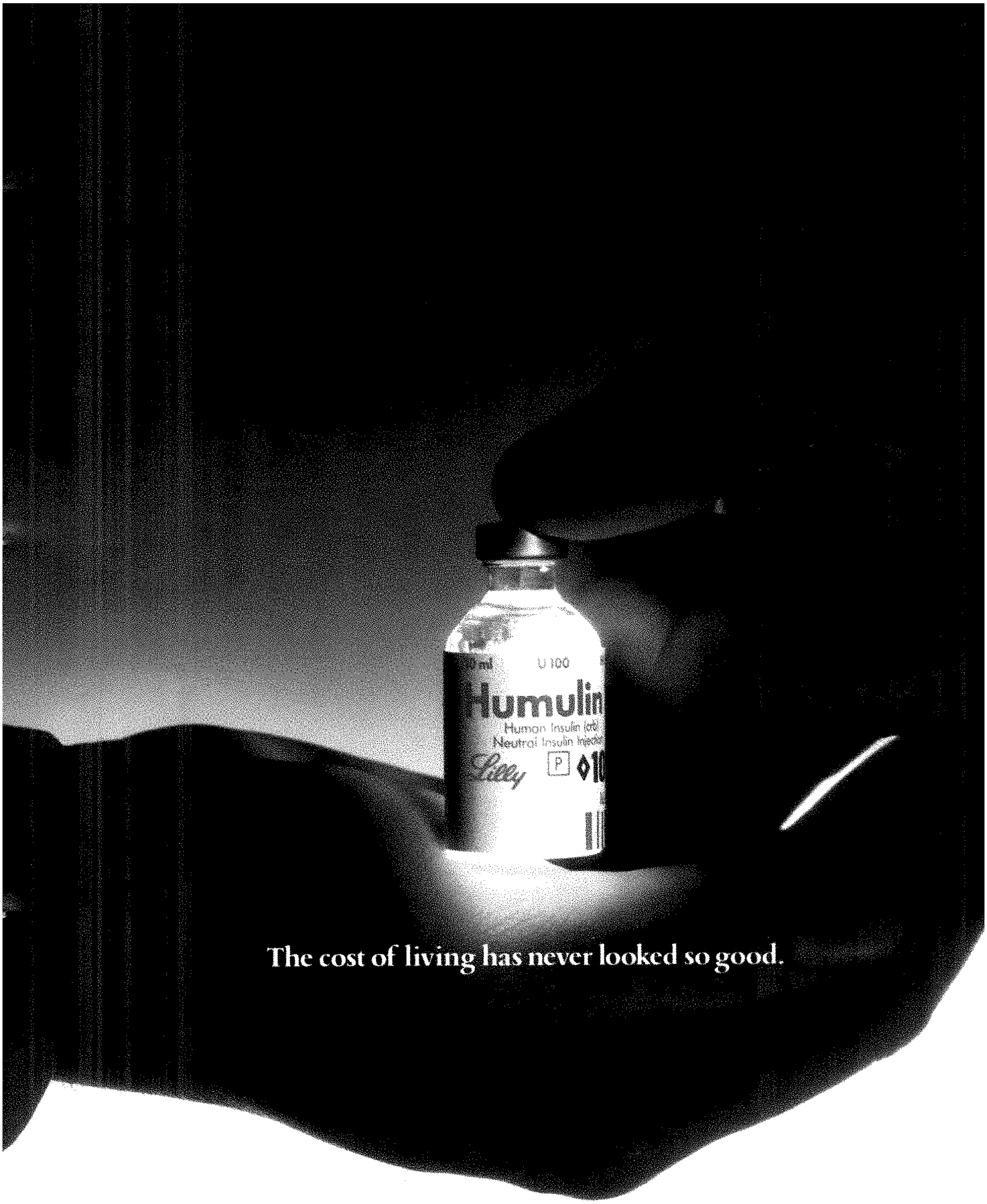
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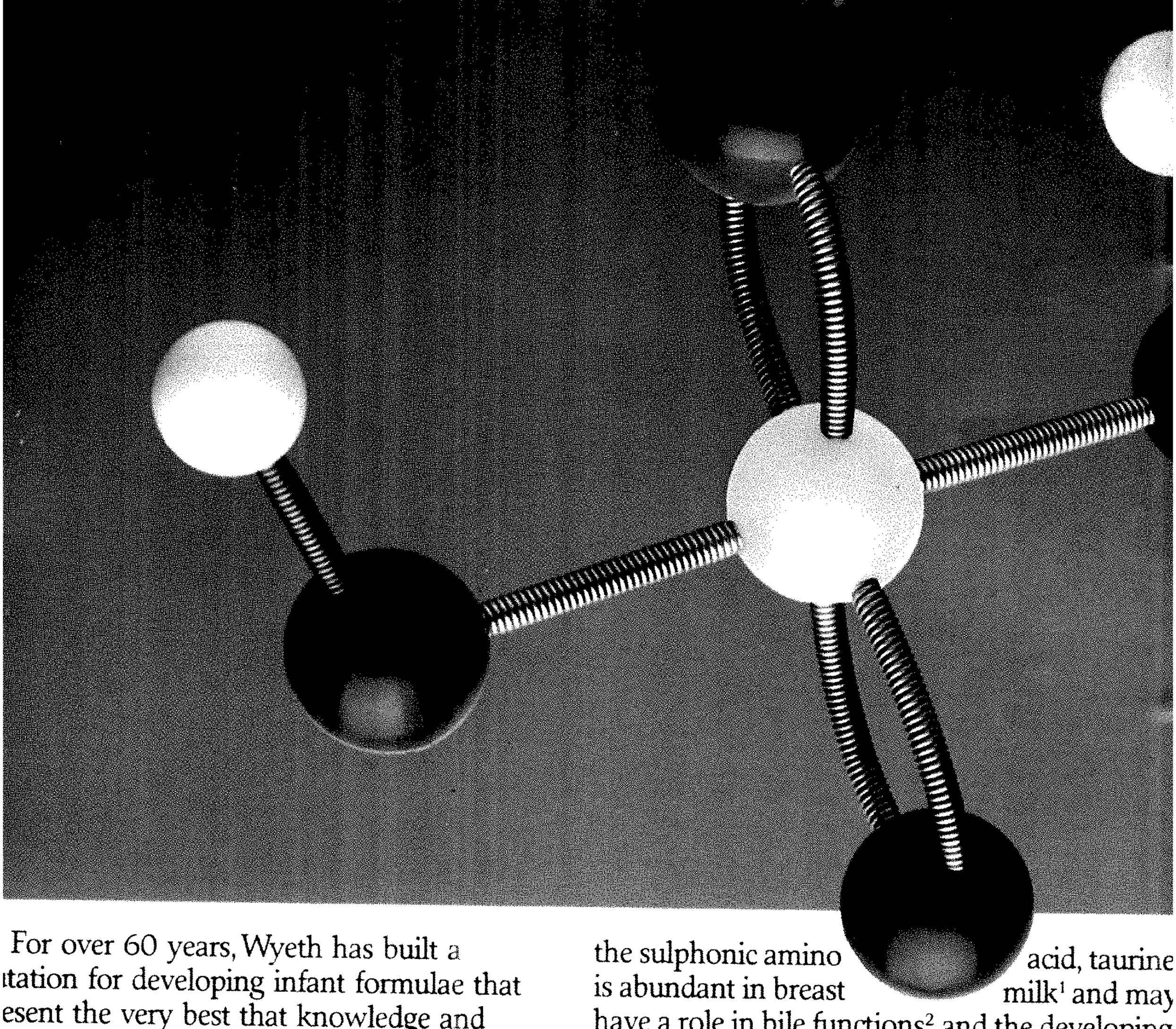

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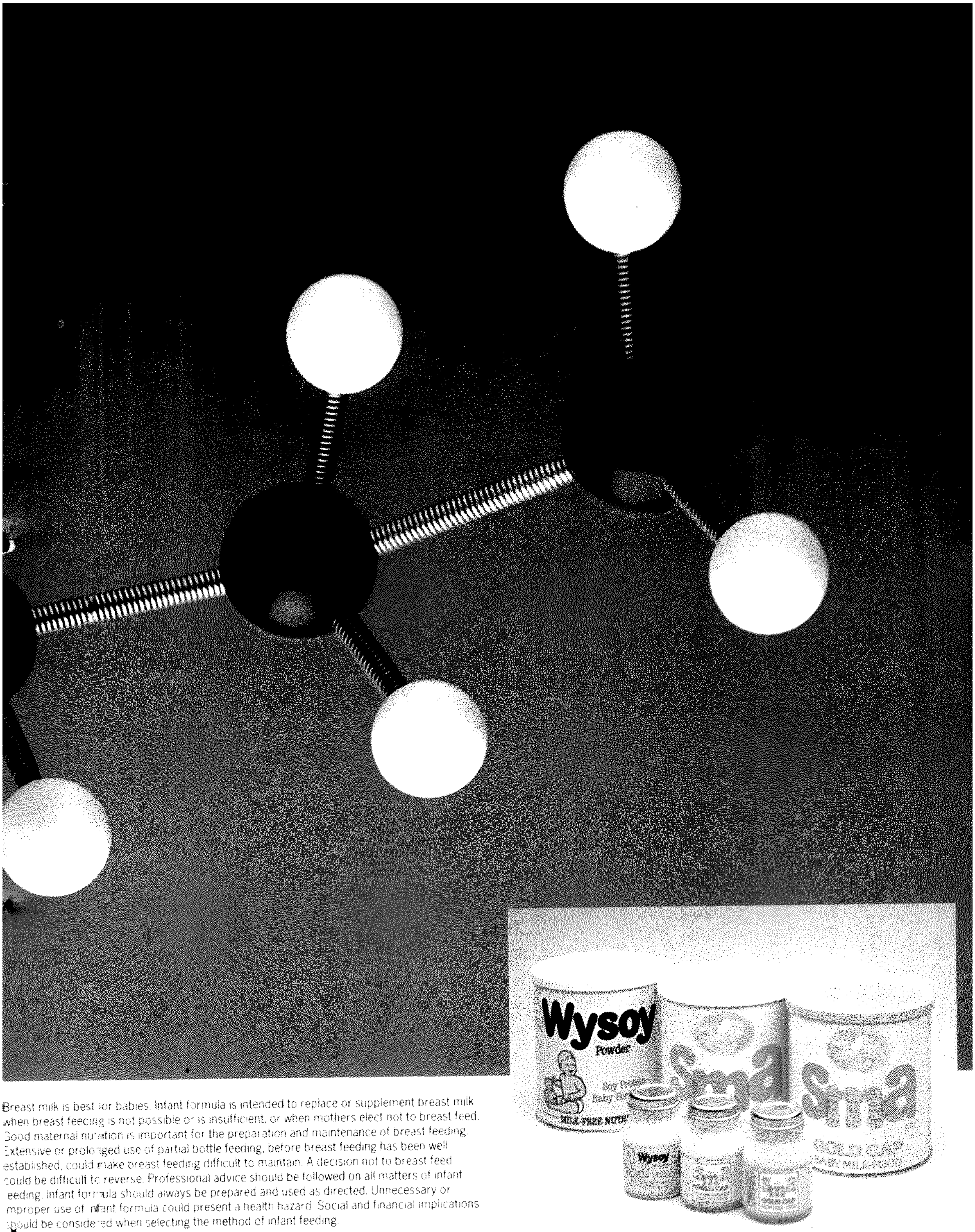

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References: 1. Rassin D.K., Sturman J.A., Gaull G.E. (1978). Taurine and other free amino acids in milk of man and other mammals. Early Human Development 2/1, 1. **2.** Jaavenpaa A.L., Rassin D.K., Kuitunen P., Gaull G.E., Raiha N.C.R. (1983). Feeding the low birthweight infant: II Diet influences bile metabolism. Paediatrics 72, 677. **3.** Sturman J.A., Gaull G.E. (1976) Taurine in the brain and liver of the developing human and rhesus monkey. In: Huxtable R., Barbeau A. (eds). Taurine. Raven Press, New York, pp 73-84. **4.** Sturman J.A., Wen G.Y., Wisniewski H.M., Neuringer M.D. (1984). Retinal degeneration in primates raised on synthetic infant formula. Int. J. Dev. Neurosci. 2, 121. **5.** Huxtable R.J., Sebring L.A. (1983). Cardiovascular actions of taurine. In: Kuriyama K., Huxtable R.J., Iwata H. (eds). Sulfur Amino Acids Biochemical and Clinical Aspects. Alan R. Liss, New York, pp 5-37.

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tart at 600mg/daily increasing by 200mg
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hildren over 20kg: Initially 400mg/day
ith spaced increases until control is
chieved. (Usually within the range
0-30mg/kg body weight per day)
hildren under 20kg: 20mg/kg of body
eight per day in severe cases may be
creased up to 40mg/kg day Increases
bove this only if plasma valproic acid
vels, clinical chemistry and haematological
arameters can be monitored **Combined
herapy** It may be necessary to raise the dose
hen used with anticonvulsants which induce
er enzyme activity Dosage of barbiturates
ould be reduced if sedation is observed
ptimum dosage is mainly determined by
izure control and routine measurement of
asma levels is unnecessary **Contra-
dications, Warnings; Contra-indication**:
ctive liver disease **Side effects**: Liver
sfunction including hepatic failure resulting
fatalities has occurred in patients whose
eatment included valproic acid or sodium
lproate The incidents mainly occurred during
e first 6 months of therapy Clinical symptoms are
ore helpful than laboratory investigations
the early stages of hepatic failure The
nset of an acute illness especially
ithin the first 6 months, which may
clude symptoms of vomiting,
thargy or weakness, drowsiness,
orexia, jaundice or loss of seizure
ontrol is an indication for immediate
ithdrawal of the drug Evidence to
ate does not establish which
vestigation could predict this possible
dverse effect measurement of liver
nction should be performed in the
st 6 months of therapy in those who
em most at risk Hyperammonaemia
ithout hepatic damage can occur, it is
sually transient, but may occasionally
esent clinically If so Epilim should be
scontinued Valproic acid inhibits platelet
ggregation Thrombocytopenia has been
ported Spontaneous bruising or bleeding
an indication for withdrawal of medication
ancreatitis, tremor, weight gain, transient
ir loss, increased alertness, aggressiveness
peractivity, amenorrhoea, stupor and oedema
ave been reported **Drug Interactions** Epilim
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Annotations

Haemophilia, blood transfusion, and the AIDS virus

After the near hysterical publicity given to haemophiliacs who have antibodies to the acquired immune deficiency syndrome (AIDS) virus, anyone might be forgiven for supposing that childhood exposure to human T cell lymphotropic virus (lymphadenopathy associated virus) (HTLV III (LAV)) is confined to patients receiving blood or blood products. This is of course not so, and in the United States the great majority of seropositive children have acquired the virus from their infected mothers during the perinatal period.[1] As the AIDS experience of the United Kingdom seems to be following that of the United States with about a three year time lag, the same may be true here by 1987.

The reason that haemophiliacs have so far occupied centre stage is twofold—they were the first group of UK children to be exposed to HTLV III by way of imported factor VIII concentrate, and they form a small, well defined population that happened already to be under close medical surveillance. By fortuitously becoming an ideal pilot group for study, they have also unfortunately become the focus for a great deal of publicity and inflated debate involving moral, ethical, and even philosophical issues, which have rather tended to obscure the size and actual nature of the medical problems involved. There is a touch of irony about this in that the fuss is reaching a climax at a time when the incidence (as opposed to the prevalence) of transfusion transmitted HTLV III infection has hopefully dwindled to zero. Large pool blood products are now nearly all processed in some way to remove or inactivate the virus, and blood donations in the UK are being tested for anti-HTLV III before being issued. Nonetheless, before such precautions were introduced, boys with haemophilia *did* become infected, and this annotation is an attempt to reflect on how many there are and the problems they present both to themselves and their contacts. In addition, there may be a tiny number of UK children infected by blood products given for reasons other than haemophilia or allied disorders. What follows is equally relevant to them.

The prevalence of transfusion transmitted HTLV III infection

According to the Haemophilia Centre Directors' annual returns, it seems that there are presently around 900 boys aged under 15 in the UK with classical haemophilia. The proportion of them who have antibodies to HTLV III is not known for certain, but on data currently available the total is tentatively estimated to be around 170 (19%). Such an overall figure has to be immediately qualified, however, as it is influenced by three important factors. Firstly, it varies considerably in different parts of the country according to the type of factor VIII replacement therapy given. The highest numbers are being seen where large pool factor VIII concentrate from several sources has been used and the lowest where only cryoprecipitate from single donors or concentrate made by the UK transfusion service has been given. Secondly, it varies according to age, with those aged under 5 showing a lower seroconversion rate than the 10–14 year olds. Thirdly, it varies with disease severity, with those most severely affected having a higher seroconversion rate than the more mildly afflicted patients. All three factors may merely relate to the amount of antigenic exposure experienced.

The figure also has to be qualified by saying that the final total will probably be higher, partly because the estimate is an extrapolation from incomplete data, and partly because, although virus transmission by transfusion had more or less ceased by the time the survey was done on which it is based, not all exposed individuals would have necessarily seroconverted by then. Under experimental conditions the time from exposure to seroconversion in chimpanzees is thought to be around 10–12 weeks,[2] but humans, receiving a smaller inoculum, may well take longer.

For the 200 British boys with Christmas disease the seroconversion rate so far seems to be much lower—less than 2%. The main reason for this is presumably that little imported factor IX concentrate has been used in such patients, who have mostly only received material from UK volunteer donors.

The consequences of transfusion transmitted HTLV III infection

The proportion of individuals exposed to HTLV III who will never show any overt symptoms of infection is not yet clear, but in haemophiliacs it seems to be large, over 80%, with positive serology being the only legacy of exposure long past the median incubation period of AIDS.[3] As antibodies to HTLV III are non-neutralising, long term virus carriage is also assumed to occur in such patients, so for the present they are regarded as potentially infective.

For the less fortunate few a number of other unpleasant sequelae might arise, and several syndromes other than frank AIDS follow HTLV III infection. Some are acute, occur shortly after exposure, and include a glandular fever like syndrome and an encephalitis, but more commonly HTLV III associated disease is chronic, producing lymphadenopathy, weight loss, night sweats, and thrombocytopenia, forming, with associated lymphocyte abnormalities, the so called AIDS related complex (ARC). Up to the autumn of 1985 no UK children with haemophilia were reported to have developed frank AIDS, though a few had developed other HTLV III associated disease, and based on adult experience it is probable that some will, in time, develop opportunistic infections.

The risks associated with HTLV III infected children

The risks associated with HTLV III infection can be considered in two categories: those encountered by the infected child and those experienced by his contacts.

Risks to the infected child centre around potential immunodeficiency and susceptibility to opportunistic or overwhelming infection. There may be a case for passive immunisation after exposure to chickenpox or measles, and live vaccines should also be avoided, but the benefits of attending school far outweigh the risks, and no seropositive children should be kept at home for their own protection.

As for risks to contacts, it is here that a sense of perspective is hardest to achieve. Based on present evidence the risks of casual transmission of HTLV III by young children to playmates at school or at home seems to be negligible. At the time of writing not a single documented case of HTLV III infection had apparently been acquired in such a way, either in the UK or the USA. Similarly, several studies on families with HTLV III seropositive members had all failed to show virus transmission between members unequivocally arising outside the context of sexual or perinatal transmission.[4]

Given such low risks, do any precautions need to be taken with the child who is positive for HTLV III? This question is often asked by teachers, family members, nurses, health visitors, and social workers, not to mention community paediatricians, school medical officers, general practitioners, and dentists. It is tempting to say no, but it is hard to give an unequivocal answer. As HTLV III is present in blood, saliva, and tears, it could be argued that anybody exposed to such substances from an infected boy is theoretically at risk. Government guidelines are somewhat confusing because those given to hospitals and laboratories handling samples from HTLV III positive patients suggest the use of gloves, gowns, and eye protection, whereas those given to seropositive individuals at home inconsistently recommend only that toothbrushes or other implements that could become contaminated with blood should not be shared and that accidents involving blood spillage should simply be cleaned with household bleach.[5]

Where does common sense end and panic begin? It must be stressed again that HTLV III is only known to be transmitted sexually, perinatally, or by direct inoculation. It is because of the latter risk that hospital personnel are advised to take such elaborate precautions, though many experts privately admit that provided good medical techniques are practiced on all patients the HTLV III carrier poses no special threat.

On balance it seems that all that is required on the domestic and social front is attention to good hygiene, and certainly no attempt to isolate seropositive children is justified. If so, another difficult question arises—who needs to know that a given boy is seropositive? Again the answer is not simple, partly because of the circumstances pertaining to adult non-haemophilic seropositive individuals, where confidentiality has to be maintained under the 1974 National Health Service Venereal Disease Regulations, and partly because of the lay public response to the discovery that boys are seropositive, which tends to make them latter day lepers.

To avoid unnecessary distress, at present most haemophilia centre directors confide information about the HTLV III state of their patients to others strictly on a 'need to know' basis, tailoring the dissemination of information to the individual patient. This would usually (though not always) include the general practitioner and usually (though not always) exclude the headmaster. It would invariably include the parents, together with a lengthy explanation of what the finding means, what it does *not* mean, and who in turn should be told by them if the need arises, such as dentists or staff at haemophilia centres other than the patient's own. Older boys would need to be told themselves, particularly if the question of sexual activity is relevant. For them the risk of disease transmission is real and detailed advice on sexual behaviour is required.

Conclusion

In such an emotionally charged area it is probably helpful to hang on to facts rather than feelings, and summarise by emphasising the following points. First, only a small number of children in the UK have evidence of transfusion transmitted HTLV III, nearly all older, and nearly all severely affected haemophiliacs. Secondly, it seems only a small proportion (as yet unknown) of these infected children will develop frank immune deficiency, and even if they do they will simply become more of a risk to themselves, not others. Thirdly, although the virus is known to be present in blood, semen, saliva, and tears, disease transmission has not yet been reliably documented from saliva or tears, or from domestic or social contact. Finally, the incidence (as opposed to the prevalence) of transfusion transmitted HTLV III infection should now be nil. If the American experience is anything to go by, perinatally transmitted disease will command the paediatrician's attention next.

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Open or closed incubators

Definitions

According to the *Oxford English Dictionary*, to 'incubate' means 'to sit upon the eggs in order to hatch them'. In this wide sense a neonatal unit might be viewed as an incubator for preterm infants. The question 'to whom is it open and to whom is it closed?' is important, though perhaps not what the editors had in mind for this annotation. The relevant *Oxford English Dictionary* definition of 'incubator' is 'an apparatus for rearing children born prematurely'. We might infer from both definitions that a protected, warm, controlled environment is necessary to rear young until they are ready for independence, though neither mentions specifically either temperature or heater.

Why incubate?

All babies have to produce heat as a byproduct of metabolic activities, and if body temperature was our only concern we could maintain this by insulation with clothing and bedding, without strict control of environmental temperature. In our anxiety to give adequate observation and attention to sick, premature infants we may choose to nurse them naked on open surfaces. If body temperature is to be maintained without extra metabolic demand we must provide the infant with the controlled 'personal climate' of a heated incubator. Those who are concerned with improving neonatal care know instinctively that the open surfaces, bright lights, and noise are unnatural, and yet babies survive. Indeed, we take comfort in the improving survival rates. From this it would seem only fair to conclude that current incubating systems satisfactorily perform their basic task, at least for most infants.

Apparatus

Two types of incubator are in common use, differing largely in the way they control heat exchange. In the 'closed' incubator, warm air is blown through a canopy around the baby, with the temperature of the air controlled either directly by the user or indirectly by servocontrol of the baby's skin temperature. In the 'open' incubator, or radiant warmer, the baby is placed on an open surface with a radiant heat element fixed horizontally above, and the heater output is servocontrolled from skin temperature. The inner walls of the closed incubator are usually a few degrees cooler than the warmed air, thus the baby loses most heat by radiation to the walls, with low convective losses. By contrast, convective losses are very high under the radiant warmer because the surrounding air is virtually at room temperature. Radiant heat is gained by skin surfaces that face the heat element and lost by other surfaces, giving a net radiant gain.

Preterm infant

For infants born at 28 weeks' gestation or more, both systems are undoubtedly capable of providing adequate and equivalent *physical* environments, in terms of environmental temperature and net heat exchange. However, the 'personal climates' are clearly different, and they are not judged as equivalent by babies. There are many reports of significantly increased insensible water loss under radiant warmers.[1–5] Studies have also shown that small babies have a slightly[4 6] or significantly[5 7] higher rate of metabolic heat production under an open warmer than in a closed incubator. However, babies showed no difference in metabolic rate between a conventional closed incubator and one with a heated canopy.[8] It seems, therefore, that some feature of the open warmer system, but not radiant heat itself, increases metabolism—even though the baby can 'demand' heat through the servocontrol system. Our suggestion is that the pronounced fluctuations of the incident radiation[5] and the spatial asymmetry under the open warmer are uncomfortable. Adults dislike pronounced asymmetry, and we have no reason to assume that babies differ.

We do not know whether the differences in water loss and metabolic rate are clinically (as opposed to statistically) significant, but if we work on the assumption that minimal water loss and energy cost are desirable then the closed incubator performs its primary task better than the open warmer.

Our practice is to nurse premature babies in closed incubators without servocontrol. Whenever possible they have the thermal and social benefit of at least some clothing—bonnets, 'preterm' jumpsuits, dresses, and smocks. Clothing can confuse the operation of a servocontrol system if this has been designed correctly for a naked baby.

Very preterm infant

The above applies to infants with water tight skins.

Infants under 28 weeks' gestation have leaky skins in the first few weeks of life and as a consequence have high evaporative water and heat losses. These are the infants for whom control of the personal climate is most crucial, but their vulnerability makes detailed experimental study impossible.

Neither closed incubator nor open warmer provides an acceptable environment when used in the conventional way. The former fails to keep the infant warm, because 'safety' standards prohibit air temperatures that are sufficiently high. The latter increases the already serious water loss.[5]

Currently, we nurse such infants in a high humidity for the first week or so of life to reduce evaporative water loss and clothe them wherever it is possible with bonnets, smocks, nappies, bootees, etc.

Personal space

Concern about the inadequacy of current incubators has led to modifications, canopies within canopies, high humidity, plastic sheets, and clothing within closed incubators; and shields, plastic sheets, and heated nursing surfaces under open warmers.[9-13] All alter the thermal environment and may introduce their own hazards; most make the system more 'closed' with respect to access to the baby.

The time has come for a radical redesign of incubators, not just 'Do it yourself' modifications, but this has to be thought out in the context of redesigned neonatal units. We must stop the 'personal climate' from dictating the design of the 'personal space'.

The requirements of the ideal 'personal space' for a preterm infant are challenging and conflicting. The surrounding gases should be under sensitive and rapid control with respect to oxygen content, humidity, and temperature, and the temperature of all surrounding surfaces should be controlled. Light and noise levels should be measured, excesses avoided, and possibly background levels cycled. The infants need support but minimal handling, protection but easy access. For some activities (nursing, medical, and social) the space needs to be 'open', for others it should be 'closed'. This may well involve adjustable heated canopies.

The whole should be a great deal more sympathetic to infants, parents, and nursing staff than it is at present. We must use our technical skills to make our neonatal nurseries more effective, but also more homely.

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Original articles

When are we diagnosing growth hormone deficiency?

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SUMMARY The height and age at presentation of 458 children beginning treatment with growth hormone between January 1980 and June 1984 were retrospectively analysed. Three hundred and nine children with isolated growth hormone deficiency had a mean (SD) age of 10 (4·1) years on beginning treatment and a mean (SD) height standard deviation score (SDS) of −3·73 (0·93). One hundred and nine patients with hypothalamopituitary tumours began treatment with growth hormone on average 3·3 years after diagnosis of the tumour and at a mean (SD) height SDS of −2·42 (1·49). In both of these categories the height SDS showed a considerable improvement compared with previous reports. Forty two patients with growth hormone deficiency secondary to cranial irradiation started treatment with growth hormone on average 6·1 years after treatment for their tumours and had a height SDS of −2·45 (1·02) compared with that of −2·45 (0·98) seen in nine similar patients from the United Kingdom starting treatment with growth hormone between 1975 and 1978. Although closer surveillance of short children in the community is leading to earlier diagnosis of growth hormone deficiency, this could possibly be diagnosed earlier if routine screening of height was to be carried out at school entry. In addition, patients who have received cranial irradiation should be regularly measured and investigated when their height velocity becomes subnormal.

The success of growth hormone in treating short stature in cases of growth hormone deficiency is well documented.[1] Although growth hormone is currently only available for selected cases, this is likely to be a temporary state of affairs, and it is therefore important that the possibility of growth hormone deficiency is borne in mind by physicians dealing with children. As it is generally believed that the earlier replacement therapy is begun in such patients the better the prognosis for final stature,[2] a retrospective analysis was made of the heights and ages of children recently accepted for treatment with growth hormone in the United Kingdom.

Methods

The patients studied were those successfully submitted by 18 of the 19 regional growth centres for treatment with growth hormone to the Health Services Human Growth Hormone Committee from January 1980 to June 1984. Criteria for acceptance were usually a subnormal height velocity coupled with biochemical evidence of defective secretion of growth hormone in response to certain pharmacological stimuli and exclusion of other causes of these phenomena such as hypothyroidism. The patients were subdivided according to whether they suffered from idiopathic isolated growth hormone deficiency or a tumour involving the hypothalamopituitary tract or had developed an endocrinopathy as a result of cranial irradiation for other malignant disease. Patients with idiopathic multiple pituitary hormone deficiencies were not studied as they included a number of very young children with congenital hypopituitarism. The heights of patients at submission were expressed as standard deviation scores (SDS) from the mean, calculated as follows:

$$\mathrm{SDS} = \frac{x - \bar{x}}{\mathrm{SD}}$$

where x is the patient's height and $\bar{x}$ and SD the population mean height and standard deviation, respectively, at that age. The population standards used were those of Tanner and Whitehouse.[3] Patients were also subdivided according to year of submission to assess whether a trend existed toward earlier diagnosis. Statistical analysis was by unpaired *t* test and linear regression.

Results

Isolated growth hormone deficiency. Three hundred and seven patients, comprising 199 boys and 108 girls, were accepted for treatment during the study period. The overall mean (SD) height SDS for these patients was −3·73 (0·93), with a mean (SD) age of submissions of 10·0 (4·1) years. Boys were on average one year older than girls at submission (10·37 (4·04) years and 9·32 (4·2) years, respectively) but had a significantly less deviant height SDS of −3·56 (0·86) compared with −4·05 (0·98) ($p<0·001$). Parental heights were available for 301 of the patients: the mean (SD) height SDS of their fathers was −0·33 (1·14) and of their mothers was −0·4± (1·18). Only nine parents had a height SDS of −3·0 or less.

Hypothalamopituitary tumours. One hundred and nine patients with this diagnosis were accepted for treatment, of whom 57 were boys and 52 were girls. Table 1 summarises details of these patients. The interval between diagnosis of their tumour and submission for treatment with growth hormone ranged from 0·27 to 13·15 years (mean 3·27 years). No significant difference was noted beween the sexes with regard to height SDS at submission for treatment with growth hormone or the time required for this. Thirty two patients had isolated growth hormone deficiency, and although they required roughly two years longer to be submitted for treatment with growth hormone, there was no significant difference between their height SDS (−2·63 (SD 1·51)) and that of the rest of the patients (−2·34 (1·48)). No correlation existed between the duration of time from diagnosis of the tumour to submission for treatment with growth hormone and the height SDS when accepted for treatment.

Radiation induced growth hormone deficiency. Forty two patients, of whom 25 were boys and 17 were girls, were submitted with this diagnosis. Details are summarised in Table 1. The interval between cranial irradiation and submission for treatment with growth hormone ranged from 1·4 to 11·86 years (mean 6·10 years). Boys had a significantly less deviant height SDS than girls at submission ($p<0·02$). Nine patients had additional endocrinopathies, and there was no significant difference between these and the remaining patients with regard to height SDS or duration of time required for submission. A highly significant negative correlation existed between the height SDS at submission and the duration of time from diagnosis of the tumour to submission for treatment with growth hormone ($p<0·001$).

In none of the three groups was there any significant trend towards earlier diagnosis when the figures were subdivided on an annual basis.

Discussion

In this study children with idiopathic isolated growth hormone deficiency were below the first centile for height at diagnosis. A greater cause for concern is that their short stature seems to have been ignored until mid-childhood. Treatment with growth hormone is currently thought to be necessary for normal growth from birth onwards, and therefore these patients were probably always smaller than their peer group. In most cases the parents were of normal height and the patients' short stature could not therefore be explained on a genetic basis. No information was available as to how long the parents had been concerned about the child's growth, creating uncertainty as to what extent the late diagnosis was due to parental complacency. Reports of the final stature of children with growth hormone deficiency who have been treated have noted that they rarely fulfil their genetic potential for height,[2 4] and this has been attributed to delay in beginning

Table 1 *Mean (SD) height SDS, age at diagnosis of tumours, and interval between tumour diagnosis and submission for treatment with growth hormone of patients with intracranial tumours*

	Height SDS	*SD*	*Age at diagnosis*	*Interval between diagnosis and submission (yrs)*
Patients with hypothalamopituitary tumours				
All	−2·42	(1·49)	8·91 (4·84)	3·23 (2·97)
Boys	−2·53	(1·70)	8·83 (5·71)	3·11 (2·92)
Girls	−2·31	(1·22)	8·99 (3·78)	3·33 (3·02)
Patients with other central nervous system tumours				
All	−2·45	(1·02)	5·23 (3·33)	6·10 (2·78)
Boys	−2·13	(1·07)	5·58 (3·43)	6·27 (2·91)
Girls	−2·89	(0·77)	4·71 (3·21)	5·84 (2·65)

Table 2 *Comparison of current height SDS (mean (SD)) with previous publications*

	Patients with isolated growth hormone deficiency		*Patients with hypothalamopituitary tumours*	
	No	*Height SDS*	*No*	*Height SDS*
United Kingdom 1971[1]	35	−4·7 (1·1)	18	−3·8 (1·6)
Switzerland 1980[7]	30	−4·2 (1·2)	10	−2·9 (1·2)
Finland[6]	41	−4·8 (1·7)	15	−3·1 (1·6)
United Kingdom 1980–4	307	−3·7 (0·9)	109	−2·4 (1·5)

replacement therapy. It is tempting to speculate that if routine screening for short stature was to be carried out at school entry examination using simple devices such as the Oxford growth chart[5] this delay in diagnosis might be overcome. The irreversible height loss suffered by these patients, however, possibly occurs even earlier than this. If so, this would lay an extra responsibility on general practitioners and infant welfare clinics. Nevertheless, the current figures show a considerable improvement over earlier published work[2 6 7] (Table 2) in that the diagnosis of growth hormone deficiency is being made when the patients' height SDS is less deviant from the mean. It must be mentioned, however, that the data on these patients do not take into account patients who were too old at presentation to benefit from treatment with growth hormone and were on this basis either never submitted to the committee for treatment or rejected on these grounds. Inclusion of these patients would almost certainly make the results poorer than they seem at present.

The height SDS of patients with hypothalamopituitary tumours also show a considerable improvement over previous reports (Table 2). It is also noteworthy that those patients with isolated growth hormone deficiency in this group, who may initially have not been under endocrinological supervision, showed no significant difference in their height SDS compared with those with additional endocrinopathies. The current situation regarding patients with radiation induced growth hormone deficiency, however, shows more cause for concern. Unlike patients with hypothalamopituitary tumours, which are often slow growing and may affect hormone secretion long before diagnosis, patients with radiation induced growth hormone deficiency are likely to have been of normal or near normal stature at original diagnosis. The low height SDS at submission for treatment with growth hormone of these patients, however, implies that their height measurements had been crossing the centile lines for some time before appropriate investigation was begun. This is supported by the strong negative correlation between the height SDS of these patients and the interval between initial treatment and submission for treatment with growth hormone. Cranial irradiation was not clearly identified as a cause of growth hormone deficiency until the mid-1970s,[8] but it is of concern that the mean (SD) height SDS of nine UK patients submitted for treatment with growth hormone shortly after this was −2·45 (0·98), which is almost identical to the current figure. One problem facing clinicians is that the height velocity of cranially irradiated patients is often subnormal during the first year after treatment, regardless of whether any endocrinopathy is present;[9] after this, however, the height velocity of these patients should be regularly monitored and investigation begun if it remains subnormal.

The authors thank the directors of growth centres who gave permission for the submission data on their patients to be studied.

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Serum fructosamine and glycated haemoglobin measurements in diabetic control

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SUMMARY Serum fructosamine and glycated haemoglobin (HbA1) were measured in capillary samples from diabetic children and compared with samples from non-diabetic children. Glycaemic control was assessed clinically and by average daily glucose values recorded by home monitoring. Fructosamine correlated with HbA1 and with average glucose values measured over 30 days. HbA1 also correlated with average glucose values measured over 60 days. Changes in fructosamine with time tended to parallel those of HbA1, and advance indication of deteriorating or improving glycaemic control was possible by observing changes in these. Fructosamine has many advantages over HbA1 measurement such as speed, technical ease, and low cost, and is a reliable alternative to HbA1 estimation as an indication of glycaemic control.

Measurement of glycated haemoglobin (HbA1) is well recognised as a method of assessing glycaemic control in the routine management of patients with diabetes mellitus.[1-3] It is of particular value in the management of insulin dependent diabetic children.[2 4] Frequent estimations may be necessary in these patients since their glucose profiles are subject to large fluctuations, causing changes in HbA1c concentrations (in one report, of approximately 1% in a week).[5] These changes may occur through the formation of an unstable intermediate, and several methods have been described for removal of this before analysis,[6 7] including a simple incubation with physiological saline for a minimum of five hours.[8]

The fructosamine test is a method of assessing serum glycosyl-protein concentration.[9] Its measurement is an index of intermediate glucose control (one to three weeks) and is of value as a screening test for diabetes mellitus,[9] gestational diabetes,[10] type I (insulin dependent) diabetes,[11] and type II (non-insulin dependent) diabetes.[12] Measurement of fructosamine may be affected by the concentration of albumin in the specimen, although there is no appreciable change within the albumin reference interval.[13]

The present study was designed to measure fructosamine and HbA1 in capillary specimens from diabetic children and to establish reference ranges. Comparisons of the measurements with clinical observations and home glucose monitoring records were also made.

Subjects and methods

Subjects. The populations studied comprised 57 children and adolescents with diabetes (29 boys and 28 girls, age range four to 17 years) attending the paediatric diabetic clinic of the Royal Preston and Chorley and District Hospitals, and 64 other children with no history of diabetes (26 boys and 38 girls, age range 1 to 17 years) attending a general paediatric clinic. Adult non-diabetic subjects (five men and five women, age range 20 to 40 years) were also used in the study. Specimens were collected from the diabetic patients at each clinic visit (average four times, range one to seven times in a period of one year).

Diabetes management

A diagnosis of diabetes mellitus had been reached using diagnostic criteria such as hyperglycaemia, glycosuria, and ketonuria. The children studied were on a twice daily insulin regimen consisting of a combination of short and medium acting insulins in varying proportions. The insulins used were purified porcine preparations or in a few cases human insulin. Assessment of control at home was by a combination of capillary blood glucose sampling using BM20-800 sticks read visually and by urine testing with Clinitest tablets, and more recently Diabur 5000 Stix. A policy of frequent capillary blood sampling was encouraged but had to be adapted to each child's tolerance. Blood samples were collected by the children four times daily (five), two times daily (34), three or four times over two to four days (13), less than 12 times per month (four), and on no occasion (one). In addition, urine tests were performed three or four times daily (seven), between three and 20 times per week (17), occasionally (10), and on no occasion (19).

The results were recorded in a diary and the patients or parents, or both, were encouraged to adjust insulin doses according to these. They had telephone access to a specialist diabetic health visitor who could advise further on this. All children were on a controlled carbohydrate diet.

The patients were seen in the clinic at a maximum interval of three months; some requiring to attend more frequently for supervision, encouragement, and advice. At each clinic visit height and weight were measured, urine tested, random blood glucose measured, and capillary blood samples taken for determination of HbA1 and fructosamine concentrations. All patients were seen at every visit by the doctor, specialist health visitor, and dietician.

Methods.

Samples

All samples were collected into polyethylene capillary tubes containing heparin and fluoride. Capillary samples (100 µl) were collected by finger prick from the diabetic subjects and venous samples were collected from the non-diabetic subjects. Venous and capillary samples were collected simultaneously from the adult volunteers.

After centrifugation (within two hours of collection), plasma was transferred to the centrifugal analyser cups and either analysed immediately for glucose, albumin, and fructosamine or stored at −4°C before analysis. The residual cells were incubated with physiological saline to remove labile component and then analysed for HbA1.

Fructosamine

Fructosamine was determined by the method of Johnson *et al*[9] using the Cobas Bio Centrifugal Analyser[13] (Roche Diagnostics). (Within batch and between batch precision CV=<1·0%, 3·0% respectively.) Variations in assay procedures described in the published reports[9-11] make it essential that each laboratory defines its own reference intervals.

Glucose and albumin

Glucose and albumin were estimated on the Cobas Bio Analyser using hexokinase and bromocresol green respectively.

Glycated haemoglobin

HbA1 was estimated by affinity electrophoresis on cellulose acetate membranes[14] (Glyco-Phore Kit, Gelman Sciences). (Within batch and between batch precision CV=6·7%, 7·3% respectively.)

Statistical analysis

Linear correlations were estimated using the method of least squares and Student's *t* test for statistical comparison.

Results

Reference ranges for fructosamine and HbA1 are shown in the Table. There was no significant difference between fructosamine and HbA1 estimated in capillary or venous samples from adult subjects (P>0·05). It was assumed, therefore, that the same would apply in children.

There was a significant difference between glucose, fructosamine, and HbA1 in the diabetic and non-diabetic groups (P<0·001). All subjects had serum albumin concentrations within the laboratory adult reference range (mean (SD), 45 (10) g/l), and the values in the non-diabetic and diabetic groups did not differ significantly (P>0·05).

Correlation of fructosamine and HbA1. Fructosamine correlated with HbA1 (r=0·86), Fig. 1(a).

Table *Reference ranges for fructosamine and glycated haemoglobin HbA1. Values are mean (2 SD)*

Subjects	*Age range (yrs)*	*Albumin (g/l)*	*Glucose (mmol/l)*	*Fructosamine (mmol/l)*	*HbA1 (%)*
Children					
Diabetic (n=56) (capillary)	4–17	41·4 (7·2)	12·5 (10·4)	1·36 (0·88)	10·2 (6·1)
Non-diabetic (n=64) (venous)	1–17	40·5 (7·14)	4·76 (1·84)	0·59 (0·26)	5·29 (1·97)
Adults					
Non-diabetic (n=10) (capillary)	20–40	—	4·78 (2·1)	0·68 (0·12)	6·0 (2·3)
Non-diabetic (n=10) (venous)	20–40	—	—	0·69 (0·10)	5·8 (2·2)

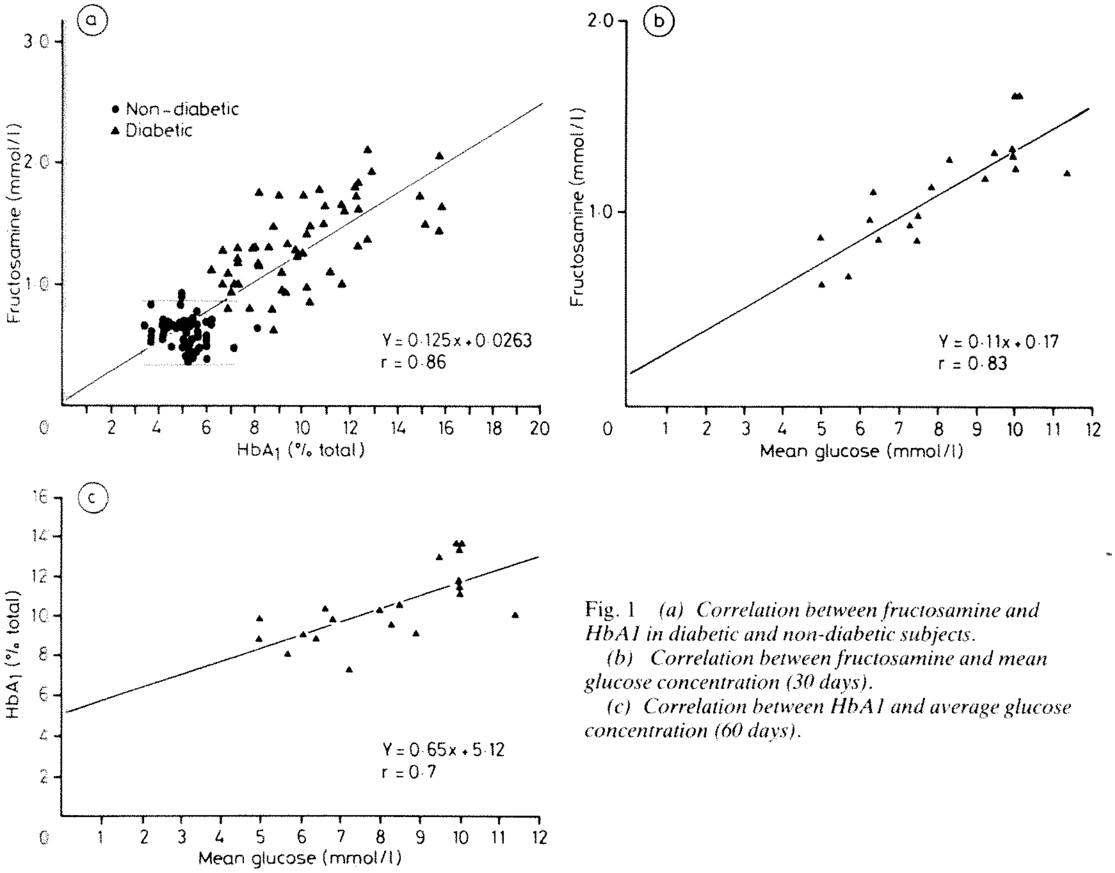

Fig. 1 *(a) Correlation between fructosamine and HbA1 in diabetic and non-diabetic subjects.*
(b) Correlation between fructosamine and mean glucose concentration (30 days).
(c) Correlation between HbA1 and average glucose concentration (60 days).

Correlation of fructosamine and HbA1 with glucose. Diabetic diaries were examined from 20 children who made an adequate number of regularly recorded home blood glucose measurements. Fructosamine correlated with the mean blood glucose value (representing, on average, 50 individual estimations) measured over 30 days before a clinic visit (r=0·83) (Fig. 1(b)). HbA1 also correlated with the mean blood glucose value (representing, on average, 110 individual estimations) measured over the preceding 60 days (r=0·7) (Fig. 1(c)).

Changes in fructosamine and HbA1. Fructosamine and HbA1 values were compared on the first and second visits in all patients, and in many instances biochemical evidence of improvement in diabetic control was seen. In general, those patients who did not perform any form of home monitoring regularly showed poor biochemical control compared with those who performed frequent daily blood tests and adjusted their insulin requirements accordingly.

Examples of serial estimations of fructosamine and HbA1 in two patients are shown in Fig. 2. Patient 1 shows fructosamine and HbA1 values above the non-diabetic ranges. These decreased during the first three months studied, approaching the non-diabetic range. Subsequent stabilisation at slightly higher values was effected. Clinical evidence of improving diabetic control was also evident, and was supported by data from the diabetic diaries. Subject 2 showed high fructosamine and HbA1 concentrations which initially tended to show improvement during the first month. Evidence of suboptimal control was subsequently shown biochemically, and in consequence intensive counselling of the patient prevented further deterioration and a return to reasonable control. The weight of this patient, measured at each clinic visit, shows good

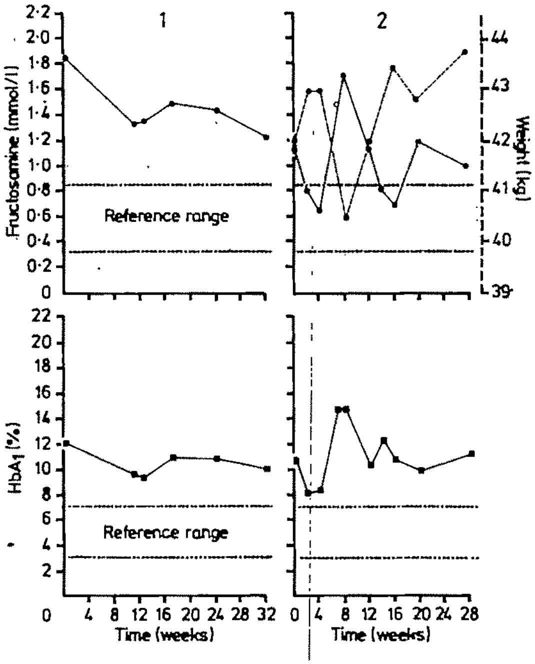

Fig. 2 *Changes over time in fructosamine (○), HbA1 (■) (for patients 1 and 2), and weight (●) (for patient 2).*

clinical evidence of varying diabetic control supporting the biochemical findings.

Discussion

Chronic hyperglycaemia may well be the cause of the vascular complications of diabetes mellitus,[15] and methods of accurate assessment of glycaemic control must surely be encouraged. This is of particular importance in children, where early and continuing stabilisation may establish a pattern of diabetic control for life.[3]

The purpose of this study was to measure fructosamine and HbA1 concentrations in capillary blood specimens from diabetic children as a measure of glycaemic control, and to compare these with clinical observations and home glucose monitoring records. Each is subject to analytical and physiological factors which may affect the estimation. For instance, the labile intermediate formed by haemoglobin and glucose in vivo and vitro[6 7] may cause overestimation of HbA1, and the presence of low serum albumin concentrations may cause underestimation of fructosamine.[13]

Fructosamine and glycated haemoglobin can be measured in the same sample of capillary blood. The reference range for plasma fructosamine in the non-diabetic group (mean (SD), 0·59 (0·26) mmol/l) is lower than that found in adults[13] (1·04 (0·4) mmol/l), which was derived from analysis of serum samples.

Fructosamine and HbA1 correlated with average blood glucose values measured by home monitoring over 30 days ($r=0·83$) and 60 days ($r=0·7$) before attending the clinic. While this correlation depends on an estimate of glucose concentration, which is relatively subjective, it serves to give a numerical expression to a wholly subjective assessment performed in clinic when the diabetic diaries are reviewed, and is therefore a relevant exercise. In our opinion, estimations of fructosamine and HbA1 at a clinic visit are valuable aids in the interpretation of the diabetic diary records.

Changes in fructosamine and HbA1 with time (for example, Fig. 2) provide a profile which, together with clinical data, gives advance warning of deteriorating or improving glycaemic control. Fructosamine is thought to reflect average glucose values over two to three weeks, while glycated haemoglobin reflects glucose values over a longer period (about six weeks). In our experience changes in fructosamine and HbA1 generally occur in parallel in stable subjects.

We believe that fructosamine and HbA1 estimations are of considerable value in the management of diabetic children. Most methods of estimation of HbA1 are, however, technically demanding, time consuming, labour intensive, and relatively costly. The method in use in our laboratory is no exception. The fructosamine assay, however, is rapid, technically simple, inexpensive, and requires small volumes of sample (20 µl). While the analytical equipment we have used is sophisticated, most district general laboratories will possess a similar or equivalent piece of apparatus, making the analysis potentially available to paediatric departments. Further studies may indicate which is the more suitable analytically and in clinical application.

We thank the staff of the paediatric clinics for their help in this study and Mrs S Jackson for preparation of the manuscript.

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Two or three insulin injections in adolescence?

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SUMMARY Morning hyperglycaemia remains a challenge to conventional insulin regimens. Eighteen adolescents participated in a one year crossover study to examine the effect of delaying the evening intermediate acting insulin from before the evening meal to bedtime. This three injection regimen caused slightly higher blood glucose concentrations in the early part of the night, and lower concentrations in the morning, but no overall change in glycosylated haemoglobin concentrations (HbA_{1c}). Seasonal change accounted for substantially more of the variance in HbA_{1c} concentrations than did the regimen change. The three injection regimen did not alter the frequency of hypoglycaemic episodes.

Metabolic control on both regimens might have been improved by more intensive monitoring and medical attention. This study suggests that factors beyond medical control, such as seasonal variation, may contribute more to the control of diabetes in adolescents than changes in conventional insulin regimens, particularly when unaccompanied by intensive monitoring.

The classic primary aims of treatment for the child with insulin dependent diabetes are to maintain normal growth and development while preventing symptomatic hypo- or hyperglycaemia.[1] As the evidence relating glycaemic control to microvascular complications has increased,[2] so the emphasis of management has been extended towards achieving normoglycaemia.[3]

One of the major barriers to glycaemic control on conventional insulin regimens is the dawn phenomenon. This consists of a rise in blood glucose concentrations that starts in the early hours of the morning and continues after breakfast, causing a mid-morning glycaemic peak.[4] Although the dawn phenomenon has been shown to be largely due to the glycaemic effects of nocturnal secretion of growth hormone,[5] it is likely to be exacerbated by the failure of conventional insulin regimens to maintain insulin concentrations throughout the night. Attempts to prevent morning hyperglycaemia by increasing the evening insulin dose may result in nocturnal hypoglycaemia, and the ensuing 'Somogyi effect' will further compromise blood glucose control.[6] Nocturnal hypoglycaemia thus limits the effectiveness of twice daily insulin regimens in controlling the dawn phenomenon.

Delaying the intermediate acting portion of the evening insulin injection from before the evening meal until bedtime has been shown to improve morning blood glucose concentrations, without increasing nocturnal hypoglycaemia, in adult patients selected because they showed a noticeable dawn phenomenon.[7] The incidence and severity of this phenomenon in childhood are not known. We have therefore performed a one year crossover study comparing the classic twice daily 'mixed' injection with a three injection regimen involving a split evening injection. The study was performed on adolescent patients because we hoped that this older age group would be more tolerant of the third injection; the notorious poor control at this time also suggested significant possible benefits.[8] Children were not selected on the grounds of glycaemic control, as we wished to establish the value of this regimen, and thus the importance of the dawn phenomenon, to the 'average' adolescent patient.

Methods

Patients. Nineteen patients were selected from the population attending the Nottingham Children's Diabetic Clinic on the grounds of age (adolescent) and duration of diabetes (>2 years) (Table 1). All children and their parents gave informed consent to the trial, which had the approval of the local ethical committee. One girl failed to comply with the trial protocol and was, therefore, excluded. Results presented are from the 18 patients who completed the trial, none of whom suffered any other major illness during the study period.

Table 1 *Patient details at randomisation*

Case No	*Sex*	*Age (decimal years)*	*Duration of diabetes (decimal years)*	*HbA$_{1c}$ (%)*	*Insulin dose (u/kg/day)*	*Post prandial C peptide* (nmol/l)*
1	M	13·4	6·8	9·8	0·87	0·01
2	M	15·5	10·7	13·7	0·90	0·02
3	F	15·7	13·7	11·1	1·08	0·03
4	F	14·6	6·6	13·1	0·99	0·02
5	M	15·9	2·4	18·1	1·00	0·06
6	F	15·1	4·6	11·7	1·10	0·03
7	F	14·5	6·1	12·1	1·04	0·02
8	M	12·7	12·0	10·0	0·90	0·01
9	M	14·4	10·7	10·9	1·07	0·01
10	F	15·2	3·2	12·7	0·96	0·02
11	F	10·8	2·5	12·6	1·24	0·03
12	F	15·8	11·0	12·6	0·77	0·01
13	F	12·2	2·3	10·9	1·12	0·16
14	F	12·0	7·4	11·8	1·26	0·01
15	F	12·8	7·8	11·0	1·18	0·02
16	F	15·2	8·1	15·7	1·30	0·02
17	M	15·8	14·2	13·9	1·37	0·02
18	M	14·8	2·2	11·1	0·76	0·02
Mean		14·2	7·4	12·4	1·05	
SD		1·5	3·9	2·0	0·17	
Range		(10·8–15·9)	(2·2–14·2)	(9·8–18·1)	(0·76–1·37)	

*Adult fasting reference range 0·18–0·52 nmol/l.

All children had normal renal function and were normotensive with no clinical evidence of microvascular complications. Only one child showed significant endogenous insulin production as shown by measurements of post prandial C peptide concentrations. Their mean concentration of glycosylated haemoglobin (HbA$_{1c}$) at randomisation (12·4%) was slightly higher than the clinic age group mean (11·8%). At entry to the study all children were being treated with injections of mixed intermediate and short acting highly purified porcine insulin, given before breakfast and before the main evening meal—a two injection regimen.

Procedure. After a four month run in period the children were randomly allocated to two groups. One group continued the two injection regimen. The other group received the trial three injection regimen: a normal 'mixed' morning injection, an injection of short acting insulin only given before the main evening meal, and an injection of intermediate acting insulin shortly before bed. After four months the children were switched over to the alternative regimen for the final four months of the study. The last child to be randomised entered and completed the study 11 weeks after the first. The total daily insulin dose, as well as the proportions taken as morning or evening, short or intermediate, acting insulin were similar on both regimens (Table 2).

Table 2 *Anthropometry, hypoglycaemia, and insulin dose in the patients when given two or three injections. All values are mean (SE)*

	Patients given two injections	*Patients given three injections*
Height gain (cm/four months)	1·39 (0·27)	1·31 (0·25)
Weight gain (kg/four months)	1·02 (0·52)	1·90 (0·42)
Hypoglycaemic episodes:		
mild	4·1 (1·2)	3·9 (0·91)
moderate	0·4 (0·1)	0·2 (0·2)
severe	0	0·1 (0·1)
Total insulin dose (U/kg)	1·03 (0·04)	1·06 (0·04)
% Total insulin doses:		
morning short acting	22·9 (1·3)	22·6 (1·3)
morning intermediate acting	40·1 (1·5)	39·6 (1·7)
evening short acting	12·0 (1·0)	13·5 (0·9)
evening intermediate acting	24·9 (2·0)	24·3 (1·7)

p=Not significant in all cases (performed by paired *t* test).

Children were seen at monthly intervals throughout the study, clinic attendances taking place at randomisation and at the end of both study periods. All other consultations took place in the children's homes. During the run in period efforts were made to improve metabolic control, with particular emphasis on reducing morning hyperglycaemia while attempting to avoid nocturnal hypoglycaemia.

Monitoring. At each consultation details of insulin dosage, diabetic symptoms, and intercurrent illnesses were recorded, and a capillary blood specimen obtained for estimation of HbA_{1c} concentrations. Children were asked to provide a four point blood glucose series (three pre prandial and one bedtime measurement) twice weekly, with midnight and 0300 measurements twice a month. Two methods of home blood glucose measurement were used: five patients used Dextrostix (Ames) read with Glucochek meters (Medistron Limited); the remainder used visually read BM 20/800 sticks (Boehringer-Mannheim). The method of measurement remained constant for each child throughout the study. During the three days before each consultation children used Sarstedt fluoride capillary tubes to provide one eight point blood glucose series (before and after the three main meals, midnight, and 0300), and two additional fasting specimens. These tubes were stored at roughly 4°C until laboratory blood glucose analysis not more than four days later.

Height and weight were measured at each clinic visit, and a post prandial specimen of blood obtained on one occasion for C peptide assay and routine biochemistry.

Laboratory methods. Blood for assay of HbA_{1c} was taken into EDTA tubes; the cells were then washed in 0·85% saline, separated, and lysed in an acid haemolysing solution within two hours of sampling. The lysate was stored at 4°C until analysed by an electrophoretic method (Gellman Sciences Inc).[9] Each specimen was analysed in duplicate, using different membranes; the means of the paired results are presented here. Blood for estimation of C peptide was taken into heparinised tubes containing Trasylol (Bayer), separated immediately, and the plasma stored at −18°C until analysed by radioimmunoassay.[10]

Questionnaire. At the end of the study all patients completed a questionnaire comparing the two regimens. On a five point scale they indicated which regimen they considered had given best blood glucose control, made them feel generally better, caused more problems with hypoglycaemia, was more convenient, and which they would prefer to continue with.

Results

Blood glucose. During the two treatment periods children performed 85% of requested home and 88% of requested laboratory blood glucose measurements. Friedman two way analysis of variance showed that no consistent changes in blood glucose profiles took place within the period of either treatment regimen. The values at individual time points did not conform to a normal distribution, and the results were therefore assessed using the median values of each child's blood glucose concentrations at each time point. Comparisons between the regimens were made using Wilcoxon's matched pairs signed ranks test.

Both the home and laboratory blood glucose measurements showed only small differences between the regimens. The laboratory measurements (Fig. 1) showed that blood glucose concentrations were lower before breakfast on the three injection regimen (p=0·03). The home measured results

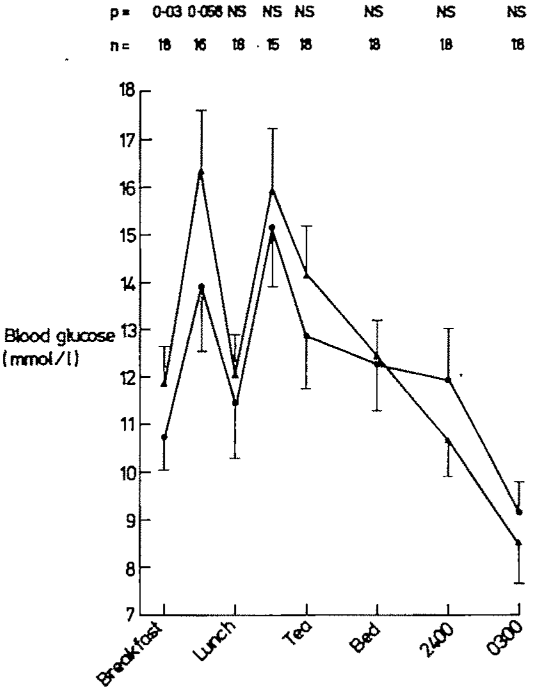

Fig. 1 *Mean (SE) concentrations of laboratory measured blood glucose on two and three insulin injections a day (p values from Wilcoxon's matched pairs signed ranks test) (▲=two injections, ●=three injections).*

showed a similar trend at this time. After breakfast blood glucose remained lower on this regimen, but this difference did not reach significance, possibly because only 16 children were able to provide sufficient samples for analysis at this time. Throughout the rest of the day blood glucose concentrations remained very similar on the two regimens, until 0300, when the home measured results showed higher concentrations on three injections ($p<0·03$). The laboratory measurements showed a similar trend at this time.

Hypoglycaemic episodes. (Table 2). These were recorded as: mild=mild symptoms rapidly relieved; moderate=made the child unwell, caused an upset to family routine; and severe=requiring admission to hospital, intravenous glucose, or glucagon. There was no difference between the regimens in any category of hypoglycaemia. Eight children experienced symptomatic nocturnal hypoglycaemia during the whole study; these episodes were slightly more common on two injections than three. Unrecognised nocturnal hypoglycaemia, defined as a home measured blood glucose concentration of less than 4·0 mmol/l (72 mg/100 ml), or a laboratory measured concentration of less than 3·5 mmol/l (63 mg/100 ml), occurred with equal frequency on both regimens. This occurred on about 10% of nights tested and affected all but two of the children during the year of the study.

Anthropometry (Table 2). The height and weight velocities on both regimens were similar.

Glycosylated haemoglobin (HbA_{1c}). The mean (SEM) values of each child's HbA_{1c} concentrations during the last two months of each treatment regimen were very similar (11·67 (0·46%) on two injections, 11·76 (0·40%) on three injections). Individual children showed clear differences in control on the two regimens, but the direction and magnitude of these changes did not correlate with age, duration of diabetes, or with randomisation values of HbA_{1c} and fasting or mid-morning blood glucose. There was, however, considerable seasonal variation in HbA_{1c} concentrations (Fig. 2), the most prominent feature of which was a fall in mean concentrations during spring and early summer.

The seasonal variation was examined further with multiple regression analysis. This method was used in order to eliminate any effect of disproportionate patient representation in the monthly summaries. All HbA_{1c} concentrations from the whole study, including the run in period, were entered, together with identifiers of the child, month of sampling, and the regimen. 'Regimen' had three values: the run in and both treatment periods. This showed that 60% of the variation in HbA_{1c} concentrations was accounted for by the differences between individual children ($p<0·001$). The addition of 'regimen' to the equation accounted for a further 0·4% of the variance (p=NS), while the addition of 'month' to 'child' accounted for a further 3·6% ($p<0·01$). There was a small interaction between month and regimen. It can, therefore, be seen that 'month' was a substantially more important predictor of HbA_{1c} concentrations than the differences between the insulin regimens.

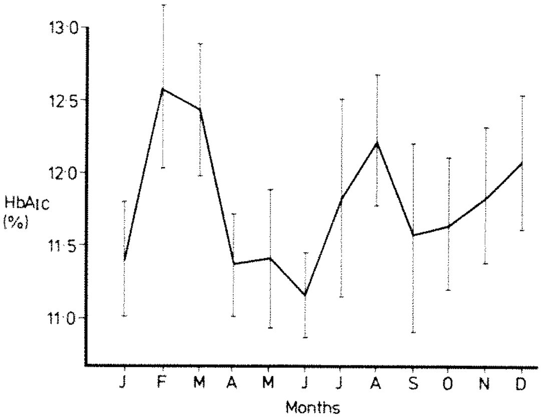

Fig. 2 *Mean (SE) HbA_{1c} concentrations from the whole study, including the run in period, by month of sampling.*

Questionnaire. In terms of blood glucose control, nine children preferred three injections, while four preferred two injections. A small majority (seven *v* five) had felt generally better on the trial regimen. Five children reported more problems with hypoglycaemia on three injections compared with two children on two injections. Thirteen (*v* two) found two injections more convenient and 11 (*v* five) opted to continue with this regimen.

Discussion

The options for improving nocturnal control on conventional insulin regimens include delaying the second injection of the day, introducing a third injection, or using an alternative delayed release preparation.[11] In a previous study, performed on younger children, we found that delaying the second injection of the day until bedtime caused some improvement in morning blood glucose concentrations but higher concentrations in the evening.[12] This suggested possible benefits from the addition of a third injection before the evening meal. This second strategy, of splitting the evening injection, has been used on adults selected on grounds of excess morning glycaemia.[7]

Nine of the 16 children who provided mid-morning blood glucose concentrations had their highest concentration of the day at this time. This figure is not quite as high as the incidence of 84% quoted for adult patients[13] but, together with examination of the overall blood glucose profiles, suggests that the dawn phenomenon is a frequent and significant finding in this age group.

The three injection regimen caused no overall change in HbA_{1c} concentrations and only small changes in blood glucose profiles. The observed blood glucose changes, lower concentrations in the morning and higher concentrations in the middle part of the night, are predictable consequences of delaying the evening intermediate acting insulin. These changes are similar to those found in the study performed on adults,using the same regimen.[7] It is tempting to suggest that patients selected on the grounds of morning glycaemia might benefit most from the trial regimen. Although the dawn phenomenon was clearly a frequent and important finding in these patients, there was no correlation between the degree of morning glycaemia and the change in HbA_{1c} concentration. Moreover, the adult study, performed on patients showing pronounced morning hyperglycaemia, also failed to alter HbA_{1c} concentrations, despite more substantial changes in blood glucose profiles.[7]

Interestingly, despite the slightly higher blood glucose concentrations seen at 0300 on the three injection regimen, no real change was observed in the incidence of either symptomatic or asymptomatic nocturnal hypoglycaemia. Winter, in a study of unselected diabetic children, found that 18% suffered asymptomatic hypoglycaemia during one night of continuous blood sampling.[14] Our incidence of about 10% of patient nights seems similar, although our patients were monitored much less intensively and at home. None of our patients had symptoms likely to be due to occult hypoglycaemia, but clearly nocturnal hypoglycaemia remains a major obstacle to conventional insulin regimens.

The finding of a seasonal fluctuation in HbA_{1c} concentrations might have been due to laboratory changes. The observed changes, however, do not correspond with any known changes in laboratory methodology, staff, or materials. Other workers, reviewing clinic HbA_{1c} results, have reported seasonal changes. Concentrations were lowest in Denmark in midsummer[15] and in Finland in spring.[16] Clinic reviews may be subject to the problem of disproportionate patient representation, but our results, in the context of a trial monitoring protocol, show a similar pattern to the Finnish children and suggest an effect of sufficient magnitude to represent a problem for research design. Further examination of this effect is in preparation.

The results of this modest intensification of treatment with insulin were disappointing and warrant comparison with the impressive results reported by others. Schiffrin and colleagues have improved metabolic control in a group of adolescents, who had previously failed to respond to two injections a day, by administering three pre prandial injections with or without a split evening dose.[17] Their patients admitted to occasionally omitting the inconvenient midday injection but performed at least four blood tests a day, a frequency that, although possibly important for optimal control,[18] would not have been acceptable to many of our patients. Of the 15 patients approached who declined participation in our study, nine mentioned the blood monitoring protocol as a deterrent, four mentioned the injection regimen, two gave no reason, and two gave other reasons.

Our patients were seen as monthly intervals, and although we encouraged them to contact us for advice between visits, few did so. Intensive medical attention can improve metabolic control,[19] and more frequent contact and more intensive blood glucose monitoring might have improved metabolic control on both regimens, perhaps particularly if coupled with an insulin dosage adjustment algorithm. Under such conditions, without the 'background noise' of poor control, greater differences between the regimens might become apparent. The results of such a study, however, could not easily be extrapolated to the general clinic setting, where this degree of individual attention is rarely possible. Our experience suggests that intensification of insulin regimens alone is unlikely to improve metabolic control without concurrent intensification of monitoring, particularly during adolescence, an age group renowned for poor and erratic control.[8]

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Metabolic rhythms in adolescents with diabetes

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SUMMARY Metabolic rhythms were studied over 24 hours in eight adolescents with insulin dependent diabetes before and two months after attempting to improve diabetic control with home blood glucose monitoring. A significant improvement in blood glucose concentration was observed, although 24 hour mean concentrations remained grossly abnormal. This improvement was accompanied by significant falls in blood glycerol and total ketone bodies concentrations and a significant rise in blood lactate concentration. Without attention to other factors affecting diabetic control, the introduction of home blood glucose monitoring produces only a small improvement in control.

Control of diabetes in adolescence is influenced by a variety of physiological and psychological factors.[1] Continuous subcutaneous insulin infusion treatment improves control in insulin dependent diabetic patients[2 3] but experience in children and adolescents is limited, and initial reports suggest that this treatment is less acceptable to these age groups.[4] Most adolescent diabetics are still treated with subcutaneous insulin regimens supported by home blood glucose monitoring.

In practice, home blood glucose monitoring is often added to the treatment regimen without a major effort being made to reform diet or exercise, both of which have profound effects upon diabetic control.

We have attempted to simulate this situation in adolescent diabetic patients by studying the impact of home blood glucose monitoring upon control as assessed by diurnal rhythms of blood glucose and other intermediary metabolites and hormones which are known to be abnormal during treatment of insulin dependent diabetes.[5]

Patients and methods

Patients. Eight insulin dependent adolescent patients (three boys) were studied. Their ages ranged from 10·8 to 15·5 years (mean 12·7 years), and duration of diabetes was from 3·8 to 6·3 years (mean 4·9 years). Patients were not included if, on clinical and biochemical evidence, they were in the 'honeymoon' period of diabetes, or in partial remission.[6] Six patients were taking twice daily mixtures of short and intermediate acting insulin (Velosulin and Insulatard, Nordisk, or Actrapid and Monotard, Novo Laboratories) and two were taking once daily mixtures of Actrapid and Monotard. At recruitment into the study none of the adolescents was using home blood glucose monitoring . The study was approved by the Ethical Committee of the Central Birmingham Health Authority.

Protocol. A 24 hour metabolic profile was performed at the start of the study, immediately after recruitment and before any attempt to improve control. After this intensive home blood glucose monitoring was done with seven point blood glucose estimations (before and two hours after main meals and before bed) using BM20–800 blood glucose strips (Boehringer) on at least one day per week. Insulin dosage was adjusted by a paediatrician or by the patient after discussion with the paediatrician on the basis of the results aimed at producing preprandial blood glucose concentrations of 4 mmol/l and concentrations of less than 7 mmol/l after meals. Changes were made in the dose of insulin but not in type of insulin or frequency of injections. Results reported by the patient were not checked by the physician. No attempts were made to influence directly dietary compliance or exercise patterns. Within eight weeks all patients reported blood glucose profiles with all values less than 10 mmol/l. A second metabolic profile was performed two months after the start of the study.

Patients were admitted to hospital the evening before the study. At 7.30 am a teflon cannula (22G Abbocath, Abbott Ireland) was inserted into an antecubital vein. Between samples the cannula was kept patent by flushing with saline (154 mmol/l). A fasting sample was taken at 8.00 am after which insulin was given. Blood samples were taken hourly until 10 pm then two hourly to 6 am. Breakfast was eaten at 8.30 am, lunch at 12.15 pm, and dinner at 6.15 pm with snacks at 10.30 am, 3.30 pm, and 9.30 pm. Evening insulin was given at 5.45 pm. The carbohydrate content of the diet and individual meals was that prescribed for regular consumption at home and was the same for the two studies.

Patients were encouraged to be ambulant between blood samples, being free to leave the ward and move between floors of the hospital.

Blood (5 ml) was withdrawn after discarding 2 ml from the cannula. Whole blood (1 to 2 ml) was mixed with ice cold 5% (v/v) perchloric acid and refrigerated immediately. The remainder was placed in a plastic tube and after clotting, serum was separated and stored at −20°C for subsequent measurement of C peptide and growth hormone.

Glucose, lactate, pyruvate, 3-hydroxybutyrate, glycerol, and alanine concentrations were measured in the perchloric acid extract by continuous flow enzymatic fluorimetric techniques.[7] Acetoacetate was measured within 36 hours in the perchloric acid extract by a spectrophotometric method.[8] Serum growth hormone was measured by a double antibody radioimmunoassay.[9] Serum C peptide was measured by a single antibody method using antibody M1230 from a commercially available kit (Novo Research Institute, Copenhagen) after precipitation of proinsulin/insulin antibody complexes by polyethylene glycol.[10] Total glycosylated haemoglobin was measured in the fasting blood sample by electroendosmosis (Corning). The normal range in our laboratory is 5·8 to 8·5%.

Student's *t* test for paired samples was used to compare glycosylated haemoglobin concentration, insulin dose, and fasting concentrations of metabolites. Metabolic rhythm data were analysed using two way analysis of variance,[11] with data classified by study and time. For the missing hourly values during the night, the value for the previous hour was repeated. For numerical comparison of the 24 hour rhythm data in the studies an average of the 24 hour mean values was calculated. Total ketone bodies (the sum of 3-hydroxybutyrate and acetoacetate) was log transformed before analysis since the data did not fit a Gaussian distribution.[12]

Results

Total glycosylated haemoglobin concentration (mean (SEM)) decreased from 13·2 (0·4)% to 10·8 (0·7)% (P<0·05). Daily insulin dose increased in all patients. The mean (SEM) insulin dose for the first study was 1·2 (0·2) U/kg and for the second study 1·4 (0·2) U/kg (P<0·05). There were no significant

Table 1 *Fasting concentrations (mean (SEM)) of blood metabolites (mmol/l) and ratios in eight adolescent diabetic patients before (study 1) and after (study 2) improvement in diabetic control*

	Glucose	*Lactate*	*Pyruvate*	*Lactate: pyruvate*	*3-Hydroxy-butyrate*	*Aceto-acetate*	*TKB*	*3-OHB: AcAc*	*Glycerol*	*Alanine*
Study 1	15·4 (1·5)	0·93 (0·12)	0·09 (0·01)	10·8 (0·5)	0·61 (0·22)	0·29 (0·12)	0·91 (0·34)	2·3 (0·2)	0·14 (0·01)	0·26 (0·02)
Study 2	11·7 (2·6)	0·87 (0·06)	0·07 (0·01)	12·0 (0·6)	0·52 (0·27)	0·26 (0·15)	0·78 (0·42)	2·7 (0·5)	0·11 (0·01)	0·23 (0·03)
P	<0·07	ns	ns	<0·05	ns	ns	ns	ns	<0·08	ns

Statistical analysis by Student's *t* test; ns=not significant.
TKB=total ketone bodies; 3-OHB/AcAc=3-hydroxybutyrate-acetoacetate.

changes in the proportion of insulin given in the morning (63% first study, 64% second study) nor in the proportion given as quick acting insulin (32% *v* 36%).

Fasting blood glucose value was lower for the second study (P<0·07; Table 1), and the mean for the group was consistently different during the day but at no time was it less than 10 mmol/l (Fig. 1). The average 24 hour mean blood glucose concentration fell from 14·6 mmol/l in the first study to 12·6 mmol/l during the second study. Over the 24 hours there was a significant improvement between studies (F=7·20; P<0·01; Table 2).

Fasting blood lactate value was not significantly different between studies (Table 1). After breakfast and morning insulin a more noticeable increase in blood lactate occurred during the second study (Fig. 2). After the evening meal blood lactate concentration was similar. Overall blood lactate concentration was significantly higher during the second study (F=7·42; P<0·01; Table 2). Blood pyruvate followed a similar diurnal pattern to lactate, although over the 24 hours differences were not statistically significant. Both fasting lactate/pyruvate ratio (Table 1) and lactate/pyruvate ratio over the 24 hours increased significantly in the second study (Table 2).

Total ketone bodies concentration was raised at the start of both studies but fell after breakfast and insulin. Throughout the 24 hours the mean concentration was consistently lower during the second study (F=17·70; P<0·001). After 9 pm there was a gradual rise in mean blood total ketone bodies concentration, although this was less noticeable in the second study (Fig. 3). Fasting blood glycerol did not differ significantly between studies (Table 1). Throughout, the mean blood glycerol concentration was lower during the second study (Fig. 3) and the

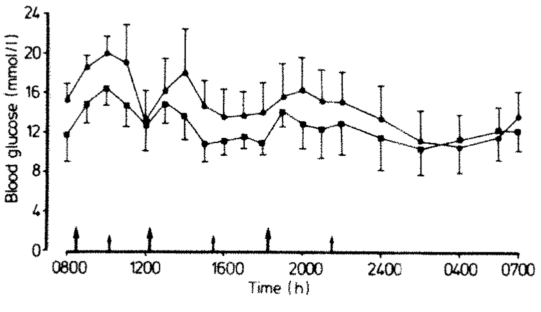

Fig. 1 *Blood glucose concentration (mean (SEM)) over 24 hours in eight adolescent diabetics before (●—●) and after (■—■) attempting to improve control with blood glucose monitoring. The large arrows indicate meals and the small arrows snacks.*

Table 2 *Average 24 hour mean (SEM) of blood metabolites (mmol/l) and ratios in eight adolescent diabetics before (study 1) and after (study 2) improvement in diabetic control*

	Glucose	*Lactate*	*Pyruvate*	*Lactate: pyruvate*	*3-Hydroxy-butyrate*	*Aceto-acetate*	*TKB*	*3-OHB: AcAc*	*Glycerol*	*Alanine*
Study 1	14·9 (2·4)	1·18 (0·05)	0·11 (0·01)	10·8 (0·5)	0·29 (0·09)	0·16 (0·05)	0·46 (0·14)	1·6 (0·2)	0·10 (0·01)	0·35 (0·02)
Study 2	12·6 (1·8)	1·39 (0·18)	0·12 (0·01)	11·6 (0·6)	0·17 (0·05)	0·12 (0·03)	0·29 (0·08)	1·4 (0·2)	0·09 (0·01)	0·36 (0·0)
F	7·02	7·42	3·29	10·20	12·38	9·26	17·70	1·72	13·67	3·58
P	<0·01	<0·01	ns	<0·01	<0·001	<0·01	<0·001	ns	<0·001	ns

Statistical analysis by 2-way analysis of variance (F=variance ratio; ns=non significant).
TKB=total ketone bodies; 3-OHB/AcAc=3-hydroxybutyrate-acetoacetate.

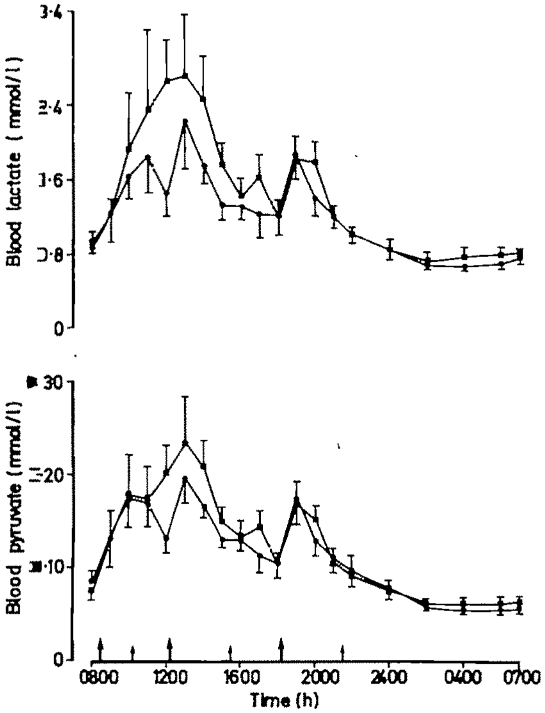

Fig. 2 *Blood lactate and pyruvate concentrations (mean (SEM)) over 24 hours in eight adolescent diabetics before (●—●) and after (■—■) attempting to improve control with blood glucose monitoring. The large arrows indicate meals and the small arrows snacks.*

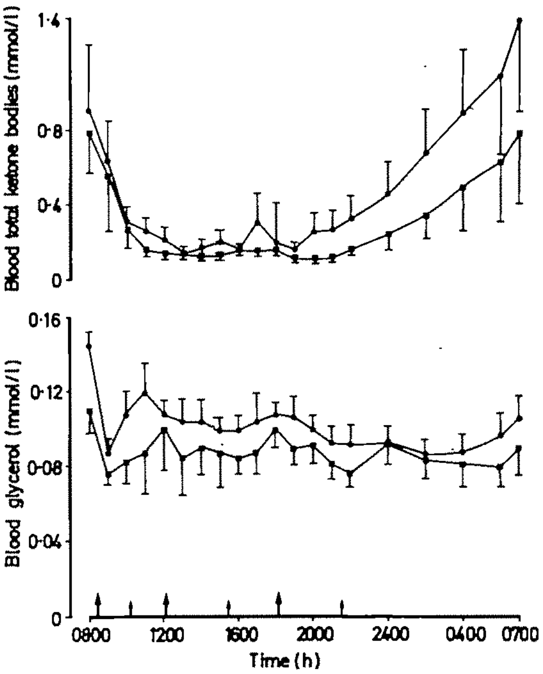

Fig. 3 *Blood total ketone bodies and glycerol concentrations (mean (SEM)) over 24 hours in eight adolescent diabetics before (●—●) and after (■—■) attempting to improve control with blood glucose monitoring. The large arrows indicate meals and the small arrows snacks.*

difference was statistically significant (F=13·67; P<0·001).

Neither fasting blood alanine nor the diurnal pattern differed significantly between studies.

One patient had no detectable C peptide during either study, and only one patient had a detectable concentration of C peptide in every blood sample. In the remaining six patients C peptide was detected in a similar number of samples during each study (maximum difference four samples). With this variation within and between patients missing values make statistical analysis problematical. Consideration of either the 24 hour mean C peptide (for values obtained) or the sum of all C peptide values measured during a study did not suggest a consistent change. An increase in C peptide was observed in three patients and a decrease in four patients between the two studies.

No significant differences were found between the two studies for serum growth hormone. The average 24 hour mean concentration of growth hormone was 32·4 mU/l during the first study (range 11·5 to 64·8 mU/l) and 29·0 mU/l (range 9·3 to 45·6 mU/l) during the second study.

Discussion

Control of diabetes during adolescence is problematical, although home blood glucose monitoring has been used to good effect—albeit in the limited situation of a diabetic camp.[13] In the present study we observed an improvement in diabetic control as assessed by the glycosylated haemoglobin and 24 hour blood glucose concentrations, although normality was not obtained with the mean blood glucose concentration never less than 10 mmol/l. The discrepancy between the patients' tests of home blood glucose monitoring and observed blood glucose concentrations is of interest. Differences between home records of blood or urine tests and glycosylated haemoglobin in this age group have been reported[14] and attributed to deliberate manipulation. Indeed some degree of observer error may be implicated with patients' readings unintentionally tending to favour lower values, although it cannot be ruled out that the performance of the study under hospital conditions may have affected the results by contributing to a decrease in daily activity. In previous rhythm studies, however, a good correlation has been found between blood glucose measurements at home and during the hospital study.[15]

Decreased activity is unlikely to explain the finding of appreciably raised fasting blood glucose concentration in both studies. Thereafter the pattern of blood glucose concentration was not grossly abnormal (Fig. 1), although the rise after breakfast was exaggerated and prolonged. A reduction in the fasting blood glucose value to normal concentrations in the present study may well have led to a near normal pattern of control.

The results for 24 hour mean blood glucose during the first study are similar to those obtained in diabetic children by Griffin *et al*[16] who also made no attempt to improve control before study. The same group, however, obtained better 24 hour mean blood glucose results after optimising blood glucose control on once or twice daily insulin injections.[15] Four of their 15 patients, however, had significant endogenous insulin secretion.[15 17]

In a previous study, Mann and colleagues[18] reported no significant differences between children who received intensive education and those who received the same degree of education and did home blood glucose monitoring. In the present study, it cannot be ruled out that the improvement in diabetic control was due to increased supervision of the adolescents rather than a direct effect of blood glucose monitoring.

Improved blood glucose control led to a significant increase in blood lactate concentration and a lesser and not significant increase in blood pyruvate concentration, with the major differences between the two studies occurring between 8 am and 6 pm. The combination of lower blood glucose with increased lactate suggests enhanced insulin stimulated glucose uptake and peripheral lactate production by the greater amount of insulin given in the second study.

The improvement in blood glucose control is reflected in the significant fall in blood total ketone bodies during the second study, although the diurnal pattern of blood total ketone bodies is not normal. Wildenhoff[19] has shown peaks in total ketone bodies occurring before meals and at 4 pm in normal subjects. In the present study, the rise in ketones before lunch was absent and blunted before dinner, and during the night there was a steady rise rather than a peak. Comparing the overnight patterns for glucose and total ketone bodies it would seem that the rise in blood total ketone bodies during the night is an earlier and clearer indication of too little insulin than the change in blood glucose.

That the lower total ketone bodies concentration is due to a decrease in lipolysis during the second study is supported by the significant fall in blood glycerol. Concentrations of glycerol obtained are within the normal range for young adults[5] despite high blood glucose concentrations. Further improvement of glucose through increased insulin administration might result in suppression of glycerol to abnormal values due to peripheral insulin administration.

In conclusion, blood glucose control was improved by a short period of home blood glucose monitoring in adolescent diabetic patients but normal values were not achieved. The fall in blood glucose concentration was accompanied by lower total ketone bodies and glycerol concentration but blood lactate concentration rose. The major stumbling block to normal blood glucose values was difficulty in obtaining a normal fasting blood glucose. Measurement of blood total ketone bodies during the night might give a clearer indication of under insulinisation. Without attention to other factors that affect diabetic control, particularly diet and exercise, home blood glucose monitoring produces only a modest improvement in control and does not restore metabolic normality.

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Neurological aspects of biopterin metabolism

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SUMMARY Plasma total biopterin concentration was measured by bioassay in 59 infants with hyperphenylalaninaemia and in 50 children with developmental regression and or movement disorder with normal plasma phenylalanine concentrations. In infants with raised phenylalanine concentrations plasma biopterin concentrations were significantly raised in proportion to the phenylalanine values. Five patients had plasma biopterin concentrations at the extremes of the range, and of these two had defective biopterin metabolism. One with low plasma biopterin concentration apparently had a partial defect of biopterin synthesis but died before investigations were complete. One with high plasma biopterin concentration, even when phenylalanine concentrations had fallen to the normal range, had dihydropteridine reductase deficiency. In this patient concentrations of homovanillic acid and 5-hydroxyindolacetic acid in the cerebrospinal fluid (CSF) were severely reduced.

In children without hyperphenylalaninaemia plasma biopterin concentrations were normal. Twenty two patients were subjected to lumbar puncture, of whom six with developmental regression without movement disorder had normal CSF biopterin concentrations, and 11 with movement disorder other than torsion dystonia had significantly lower CSF biopterin concentrations. Five patients with torsion dystonia had normal biopterin concentrations.

Tetrahydrobiopterin is the essential cofactor for three hydroxylation reactions, the conversion of phenylalanine to tyrosine, tyrosine to L-dopa, and tryptophan to 5-hydroxytryptophan.[1] These last two reactions are the rate limiting steps of catecholamine and serotonin synthesis. Deficiency of tetrahydrobiopterin, due either to defective biopterin synthesis from guanosine triphosphate or dihydropteridine reductase deficiency (Fig. 1), is the cause of hyperphenylalaninaemia in 1–3% of infants detected on routine neonatal screening.[2–5] Children with deficiency of tetrahydrobiopterin may develop progressive neurological disease, in which movement disorder is a prominent feature and which is unresponsive to a low phenylalanine diet and due in large part to deficiency of neurotransmitter amines. We wished to assess whether measurement of plasma total biopterin concentrations would help in distinguishing patients with hyperphenylalaninaemia due to defective biopterin metabolism from those with phenylalanine hydroxylase deficiency.

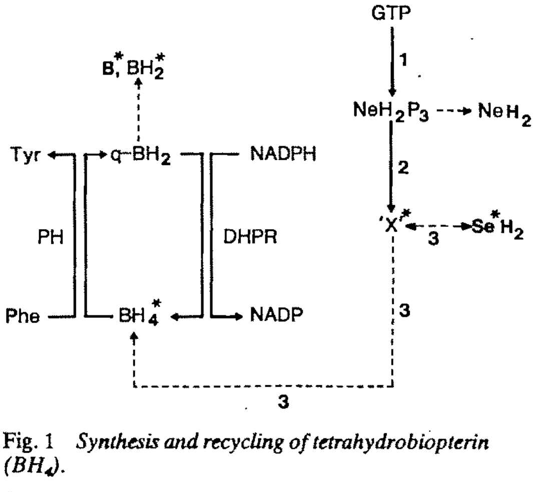

Fig. 1 *Synthesis and recycling of tetrahydrobiopterin (BH_4).*

GTP=guanosine triphosphate, NeH_2P_3=dihydroneopterin triphosphate, NeH_2=dihydroneopterin, 'X'=tetrahydroketopterin, SeH_2=sepiaterin, q-BH_2=quinonoid-dihydrobiopterin, BH_2=7, 8 dihydrobiopterin, B=biopterin, *=active in *Crithidia fasciculata* bioassay. Phe=phenylalanine, Tyr=tyrosine. Enzymes: PH=phenylalanine hydroxylase, DHPR=dihydropteridine reductase, 1=GTP cyclohydrolase, 2=tetrahydroketopterin synthesising enzyme, 3=sepiapterin reductase.

Symptomless patients with normal plasma phenylalanine concentrations, yet defective biopterin synthesis, have been described,[6] and others may have symptoms, and/or phenylalanine accumulation, only when exposed to an excessive phenylalanine intake.[7] It is not known how many children with neurological disease may be suffering from occult disorders of biopterin metabolism, and part of the present study was to assess the prevalence of such disorders among children with severe neurological disease, especially that accompanied by movement disorder. Adults with movement disorder may have reduced 'hydroxylase cofactor activity' in cerebrospinal fluid (CSF),[8 9] and there are reports of impaired biopterin synthesis in the brains of patients with senile dementia.[10]

Patients

Infants with phenylketonuria. Plasma was obtained from 53 consecutive infants detected on routine neonatal screening before introduction of the low phenylalanine diet. Seventeen were retested after a few weeks on treatment. Plasma was also obtained from six infants who had already started the diet when first seen. Five infants underwent further investigation (see below), including lumbar puncture in one patient, because initial biopterin concentrations were 'high' or 'low' (2SDs) compared with the rest of the group.

Patients with neurological disorder. These were 50 children aged 1 month to 16 years undergoing neurological investigation because of developmental regression or extrapyramidal disturbance. They were investigated with the permission of their parents and with the approval of the hospital ethical committee. All had plasma phenylalanine concentrations below 200 μmol/l (3·3 mg/100 ml), and the pathogenesis of their illness remained obscure despite extensive investigation. Five patients had torsion dystonia, four had dominantly inherited tics, 19 had developmental regression, accompanied by epilepsy in nine, and in a further 22 patients severe extrapyramidal disturbance (choreoathetosis, tremor, dystonic posturing) was a prominent feature of their illness, accompanied by mental retardation in 13 and epilepsy in eight. Plasma was also obtained from the four affected parents with dominantly inherited tics.

Methods

Measurement of total biopterin activity. Heparinised blood 1–2 ml was obtained by venepuncture, and plasma was separated by centrifugation. Between 0·5 and 1 ml of CSF was obtained by lumbar puncture using a standard technique. Specimens were frozen as soon as possible and stored at −20°C. For analysis, samples were thawed, diluted with 0·2 molar, pH 5·0 phosphate buffer 1:20, autoclaved, and assayed as described previously using *Crithidia fasciculata*.[6 11] The growth response was read against a pooled plasma blank using standards of tetrahydrobiopterin. In two patients with inborn errors of biopterin metabolism the crithidia results were confirmed by urine pterin analysis[12] (Dr A Niederwieser, Zurich; Professor J A Blair, Birmingham) using high performance liquid chromatography. Urine contains roughly 1000 times the concentrations of total biopterin compared with those in plasma.[11]

Oral load of tetrahydrobiopterin. The protocol used here was that of Niederwieser *et al.*[13] The test is carried out when plasma phenylalanine concentrations are raised. After an overnight fast 7·5 mg/kg of tetrahydrobiopterin combined with vitamin C (supplied by B Schircks, Zurich) was given on a spoon. Plasma phenylalanine and tyrosine concentrations were measured at baseline and at one, two, four, six, eight, and 24 hours, and urine, or plasma, biopterin concentrations were measured to show that the tetrahydrobiopterin had been absorbed.

Oral load of L-phenylalanine. After an overnight fast 100 mg/kg of L-phenylalanine was given dissolved in fruit juice and plasma phenylalanine; tyrosine and biopterin concentrations were measured at baseline one, two, three, four, and six hours.[6]

Assay of dihydropteridine reductase activity. This is the diagnostic test for inherited deficiency of dihydropteridine reductase activity, and the assay is now carried out on dried blood spots[14 15] in all new patients presenting with phenylketonuria at our clinic.

These procedures were not available in our laboratory until the end of the present study and liver biopsy was carried out in one patient for measurement of dihydropteridine reductase and phenylalanine hydroxylase activities by Dr F Rey, Paris.[5]

Measurement of homovanillic acid and 5-hydroxyindolacetic acid. The first 0·5 ml of CSF was placed on cardice at the bedside and stored at −20°C. Measurements were made using high performance liquid chromatography with electrochemical detection. Concentrations of homovanillic and 5-hydroxyindolacetic acids in CSF provide an approximate index of dopamine and serotonin turnover in the central nervous system[16] and have been used here to assess the central effects of disturbed biopterin metabolism. Homovanillic and

5-hydroxyindolacetic acids in lumbar CSF are higher in early childhood than in later life,[16] so results need to be compared with controls of similar age. Only limited control data were available from our own studies, but this is consistent with the data of Siefert *et al.*[16] Initially, these measurements were not available in our own laboratory, and the assays were done by Dr M Tricklebank, London.

Results

Infants with phenylketonuria. In comparison with healthy children[6] and infants with neurological disorder, plasma biopterin concentrations were markedly raised (Fig. 2). Generally, the least rise was present in the infants with phenylalanine concentrations closest to the normal range, but even in the group with phenylalanine concentrations below 400 µmol/l (6·6 mg/100 ml) the mean plasma biopterin concentration (3·16 ng/ml) was significantly raised in comparison with the mean (2·2 ng/ml) for infants under 2 months of age with neurological disorder ($t=2{\cdot}23$, $0{\cdot}02>p<0{\cdot}05$). In patients with plasma phenylalanine concentrations below 2000 µmol/l (33 mg/100 ml) there was a broadly linear relation and a significant positive correlation between biopterin and phenylalanine concentrations ($r=0{\cdot}68$, $t=2{\cdot}640$, $0{\cdot}01>p<0{\cdot}02$). At higher phenylalanine concentrations the scatter of results widened, and the linear relation was lost. The correlation between plasma biopterin and phenylalanine concentrations was closer for patients on a low phenylalanine diet ($r=0{\cdot}89$, $t=2{\cdot}941$, $0{\cdot}001>p<0{\cdot}01$).

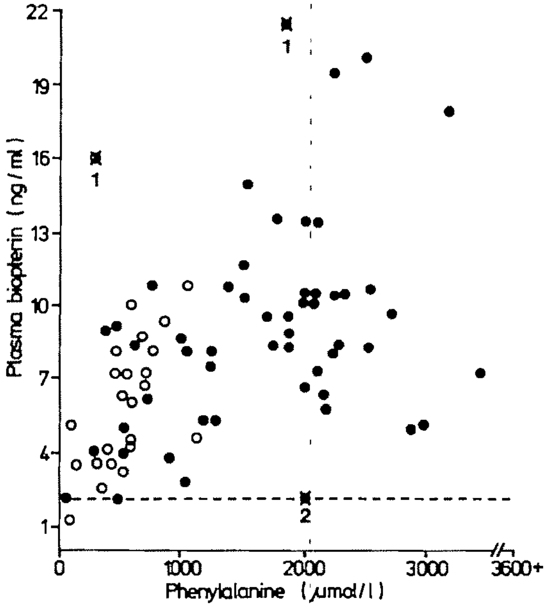

Fig. 2 *Plasma biopterins measured by crithidia assay versus plasma phenylalanine concentrations in 59 infants with phenylketonuria, pretreatment (●) and on a low phenylalanine diet (○). – – – –=Mean value of biopterin in six control infants.*

Case 1 had deficiency of dihydropteridine reductase activity, and case 2 has defective biopterin synthesis.

Conversion: SI to traditional units—Phenylalanine: 1 mmol/l≈16·5 mg/100 ml.

Five patients had plasma biopterin concentrations at or outside 2SDs from the means for other patients with similar phenylalanine concentrations (Table 1). Further investigation of biopterin metabolism in three of the five gave normal results as follows. In one patient with an initial biopterin concentration of 18 ng/ml plasma biopterin concentration fell to the normal range (2·1 ng/ml) when a plasma phenylalanine was 60 µmol/l (1 mg/100 ml), and no further investigation was undertaken. In another patient with an initial biopterin concentration of 20·5 ng/ml the value fell to 6·6 ng/ml when phenylalanine was 700 µmol/l (11·6 mg/100 ml), and an oral load of tetrahydrobiopterin produced no change in phenylalanine or tyrosine concentrations (Fig. 3), even though plasma biopterin concentrations rose during the test to 16 ng/ml. Dihydropteridine reductase activity in a dried blood spot was normal (174 µmol NADH/min/l, normal range 90–180 µmol/l).

A third patient with an initial concentration of 19·5 ng/ml was investigated elsewhere on a low phenylalanine diet and found to have a normal urine pterin pattern. The results of tests on these three patients indicated that the initial high biopterin values were due to the phenylalanine accumulation without deficiency of dihydropteridine reductase

Table 1 *Plasma biopterins (mean (SD)) according to phenylalanine concentrations in infants with phenylketonuria due to phenylalanine hydroxylase deficiency. Cases 1 and 2 omitted*

	No of cases	*Plasma biopterin (ng/ml)*	
		Mean	*(SD)*
Control infants (<2 months)	6	2·20	(0·93)
Phenylalanine range (µmol/l):			
0–399	7	3·16	(1·35)
400–799	23	6·54	(2·34)
800–1199	7	6·87	(3·09)
1200–1599	8	9·33	(3·40)
1600–1999	7	9·80	(1·76)
≤2000	24	9·79	(5·09)

One way analysis of variance $F=3{\cdot}71$, $p<0{\cdot}01$.

Conversion: SI to traditional units—Phenylalanine: 1 mmol/l≈16·5 mg/100 ml.

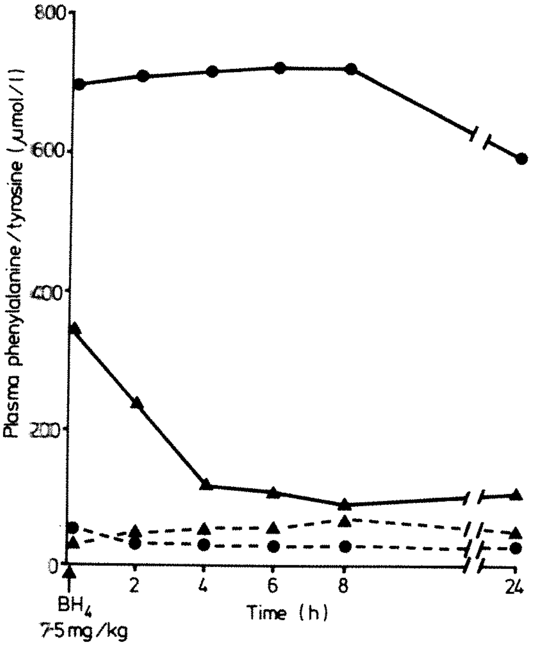

Fig 3 *Plasma phenylalanine (——) and tyrosine (– – –) concentrations after a single oral dose of tetrahydrobiopterin (BH_4) 7·5 mg/kg, in a patient with dihydropteridine reductase deficiency (▲) and in a patient with phenylalanine hydroxylase deficiency (●).*

Conversion: SI to traditional units—Phenylalanine: 1 mmol/l=16·5 mg/100 ml.

activity. Investigations in two remaining patients, who proved to have abnormal biopterin metabolism, are described in more detail below.

Case 1: deficiency of dihydropteridine reductase activity. This infant had the highest initial plasma biopterin concentration (21·6 ng/ml) of the series. When retested after phenylalanine concentrations had fallen to 240 µmol/l plasma biopterin concentration was still high at 16·0 ng/ml. These results suggested a deficiency of dihydropteridine reductase activity, which was confirmed on further investigation. Urine pterin analysis gave a biopterin: neopterin: creatinine ratio of 814 (expected value 9–32, Dr A Niederwieser), and plasma phenylalanine concentration fell from 344 to 99 µmol/l (5·7 to 1·6 mg/100 ml) while tyrosine rose from 39 to 65 µmol/l in response to administration of tetrahydropteridine. There was no detectable dihydropteridine reductase activity in the liver, although phenylalanine hydroxylase activity was normal (Dr F Rey, Paris). Concentrations of total biopterin in CSF were raised (9–11 ng/ml) (Table 2) compared with the results found in the patients with neurological disorders (Table 3), but homovanillic (19 ng/ml) and 5-hydroxyindolacetic (3·5 ng/ml) acids were markedly reduced and were not increased by a single dose of tetrahydropteridine (7·5 mg/kg) (Table 2). The patient showed only minor clinical abnormalities (hypotonia and hypomobility).

Administration of L-dopa (10–12 mg/kg), carbidopa (as Sinemet-110), and 5-hydroxytryptophan 10–12 mg/kg from 3 months of age led to a rise in the amine metabolite concentrations in CSF (Table 2) and disappearance of the clinical signs. The patient made good developmental progress for the next 18 months, although intercurrent illness caused transient hypotonia. At 10 months of age neurotransmitter replacement therapy was temporarily withdrawn during a trial of monotherapy with tetrahydropteridine at a dose of 20 mg/kg/day. After five days the patient became grossly hypotonic and developed an acute oculogyric crisis, which was reversed within hours of reintroduction of L-dopa and 5-hydroxytryptophan. Despite a rise of plasma total biopterin concentration from 11 ng/ml to 73 ng/ml during administration of tetrahydropteridine there was no rise in the already raised CSF total biopterin concentration. Concentrations of homo-

Table 2 *Neurochemical findings in case 1 with deficiency of dihydropteridine reductase activity. Treatment was with L-dopa, 5-hydroxytryptophan, and carbidopa and trial was of tetrahydrobiopterin 20 mg/kg/day*

	Pretreatment		*During treatment*				*Controls (n=6)*
	Baseline	*5 hours after tetrahydrobiopterin×1*	*L-Dopa, 5-hydroxytryptophan, and low phenylalanine diet*			*Tetrahydrobiopterin only 20 mg/kg*	*Range*
Age (months)	3·1		3·5	6	9·5	10	1–48
Cerebrospinal fluid:							
Homovanillic acid (ng/ml)	17	16	40	91	102	37	160–60
5-Hydroxyindolacetic acid (ng/ml)	5	5	48	33	38	4	80–22
Biopterins (ng/ml)	—	—	—	9	11	10	3·1–4·4
Plasma biopterins (ng/ml)	21	27	16	—	11	73	0·5–4·8

Controls=six mentally retarded children without movement disorder.

Table 3 *Plasma and CSF biopterins (ng/ml) in children with neurological disorders*

Group	*Age (yrs)*	*Biopterin (ng/ml)*					
	Mean	*Plasma*			*CSF*		
		No	*Mean*	*(SD)*	*No*	*Mean*	*(SD)*
Mental retardation	4·2	19	1·8	(1·1)	6	3·7*	(0·6)
Movement disorder	4·3	22	1·7	(0·8)	11	2·3*	(1·0)
Torsion dystonia	12·1	5	1·7	(0·3)	4	3·6	(0·8)
Inherited tics	12·1	4	2·2	(0·9)			
Total		50	1·78	(0·86)	21	2·9	(0·8)

*Difference between CSF biopterin in children with mental retardation and those with movement disorder significant ($t=6{\cdot}22$, $p<0{\cdot}001$).

vanillic and 5-hydroxyindolacetic acids fell in accordance with the clinical observations (Table 2). Peripheral phenylalanine accumulation was, however, well controlled by a daily dose of 50 mg tetrahydrobiopterin, and this treatment was continued to obviate the need for a low phenylalanine diet. Full details of this patient have been published elsewhere.[17]

Despite good control of plasma phenylalanine concentration and continuing amine replacement therapy, developmental delay and regression occurred during the third year of life with deterioration in speech, impaired balance, ataxia, pinpoint pupils, recurrent absences, grand mal fits, increased tone, brisk jerks, and bilateral extensor plantar responses. Low total folate concentrations in serum and CSF suggest that the neurological deterioration was due to interference by the accumulating biopterins with folate metabolism,[17] and administration of folinic acid (3 mg/day) halted the neurological deterioration.

Case 2: defective biopterin synthesis. A routine screening test for phenylketonuria was negative on the 10th day when the infant was receiving milk feeds but had developed diarrhoea. Raised phenylalanine concentrations, with an excess of phenylketones in the urine, was first noted at 4 months of age after the start of complete intravenous nutrition for persistent diarrhoea and failure to thrive. At this time the infant weighed only 3·6 kg, had recurrent fits, was severely delayed in development, and was noted to be grossly hypotonic with dyskinetic movements. Plasma biopterin concentration (2·2 ng/ml) was in the normal range despite plasma phenylalanine concentrations above 2000 μmol/l (33 mg/100 ml) (Fig. 2). Withdrawal of intravenous treatment led to a fall of phenylalanine to 600 μmol/l within 48 hours, but the infant suddenly collapsed and died. A dried blood spot obtained just before death showed no detectable biopterin activity, and urine analysis by high performance liquid chromatography showed a low total biopterin of 0·475 μg/ml and high normal neopterin of 5·325 μg/ml, with a biopterin:neopterin ratio of 1:11 (the normal for early infancy being 1:2, Professor J Blair). These findings suggested that the infant had a partial defect of biopterin synthesis. Permission for post mortem was refused.

Patients with neurological disorder. The mean (SD) plasma total biopterin concentration for the 50 children was 1·78 (0·86) ng/ml, almost identical to the mean (1·75 ng/ml) found in 10 normal children in a previous study.[6] There were no significant differences between groups (Table 3), and there was no relation between age and plasma biopterin. Parents with dominantly inherited tics had similar plasma biopterin concentrations (mean 2·2 ng/ml) to their children. Two patients, one with mental retardation and one with movement disorder, had initial plasma biopterin results at the lower limit of detection (0·2 ng/ml). They were investigated by means of a phenylalanine load (Fig. 4, cases 1 and 2). Fasting plasma biopterin concentrations were 1·6 and 1·3 ng/ml, respectively, and the biopterin response to phenylalanine was normal. The low initial readings may have been due to artefact, perhaps caused by delay in specimen handling.

CSF total biopterin concentrations were generally higher (overall mean (SD) 2·9 (0·8) ng/ml) than plasma values (Table 3). With the exception of four children with torsion dystonia, however, patients with movement disorder had a significantly lower mean CSF biopterin (2·3 ng/ml) than the mean for six mentally retarded patients without movement disorder (3·7 ng/ml, $t=6{\cdot}22$, $p<0{\cdot}001$), and in five out of 11 patients with movement disorder CSF biopterin concentration was below plasma biopterin concentration. In five patients with torsion dystonia CSF biopterin concentrations were similar to those in children without movement disorder.

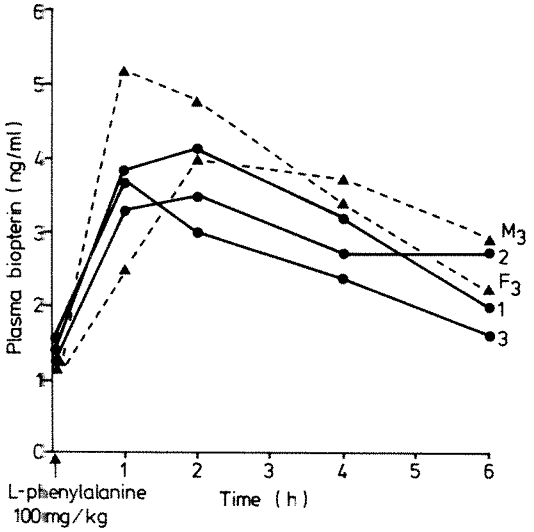

Fig. 4 *Plasma biopterins after a load of L-phenylalanine, 100 mg/kg in three patients with neurological disorders: 1 = extrapyramidal disorder, 2 = mental retardation, and 3 = torsion dystonia.*

M_3 and F_3 = mother and father of case 3. Plasma phenylalanine concentrations rose to between 420 and 601 μmol/l (6·9 and 9·9 mg/100 ml).

Conversion: SI to traditional units—Phenylalanine: 1 mmol/l ≈ 16·5 mg/100 ml.

Patient with torsion dystonia. One patient who had normal plasma and CSF biopterin concentrations was investigated in more detail because of a previous report[9] of reduced hydroxylase cofactor activity in CSF in members of two families with dystonia.

This patient presented with left intermittent torticollis at 3 years of age. At 9 years he exhibited a severe dystonic posture of the neck, worse in the afternoon after eating, and disappearing during sleep. He also had long standing swallowing difficulty. He had a positive glabella tap and intermittent torsion dystonia of the left foot. Although he was of above average intelligence, he had great difficulty with handwriting, during which he adopted a bizarre posture. Neurological examination did not show any other abnormalities. On radiological examination there was atony and gross dilatation of the oesophagus with complete absence of peristalsis and failure of relaxation of the lower oesophageal sphincter. There was no reflux, and the picture resembled severe achalasia of the cardia. A fasting plasma phenlalanine:tyrosine ratio was <1 in patient and parents, indicating that there was no major impairment of phenylalanine hydroxylation in the liver. The response of plasma biopterin, phenylalanine, and tyrosine concentrations to a phenylalanine load in patient and both parents (Fig. 4) was normal. Assay of dihydropteridine activity in a dried blood spot from the patient was also normal (102 μmol NADH/min/ml). CSF homovanillic (38·5 ng/ml) and 5-hydroindolacetic (8·4 ng/ml) acids seemed to be low, although not as strikingly so as in the patient with deficiency of dihydropteridine activity. Therapeutic trials of Tegretol and of modest doses of Sinemet-110 (half a tablet thrice daily) with 5-hydroxytryptophan (20 mg thrice daily) produced no improvement in symptoms, and the latter treatment caused unacceptable drowsiness. Finally, bromocriptine in a dose of 2·5 mg twice a day abolished all symptoms over the course of four months. The swallowing difficulties gradually resolved, and the radiological abnormalities disappeared completely. After one year bromocriptine was withdrawn in a double blind manner over a six month period without causing clinical relapse, and six months later the patient remains perfectly well.

Discussion

The results reported here indicate that measurement of plasma total biopterin activity is of value in the diagnosis of patients with hyperphenylalanine due to tetrahydrobiopterin deficiency. The disadvantages of the crithidia assay are that some biopterin activity is lost in the course of the assay, it does not distinguish the different species of biopterin, and it does not measure neopterins. Newer methods of pterin analysis using high performance liquid chromatography[18 19] and radioimmunoassay[20] can be used to measure the different species of biopterin and neopterin. There will, however, be a continuing need for simple, sensitive, and cheap methods of biopterin measurement for routine testing of infants with phenylalanine accumulation. The crithidia assay can also be applied to dried blood spots, making routine testing even simpler.[15]

The results of the present study, showing that infants with raised plasma phenylalanine concentrations due to deficiency of phenylalanine hydroxylase activity have raised plasma biopterin concentrations in proportion to the hyperphenylalaninaemia are consistent with other studies.[6 15] Among 59 consecutive infants with persistently raised plasma phenylalanine concentrations two patients, both with plasma biopterin concentrations 2SD from the mean for patients with phenylalanine hydroxylase deficiency (allowing for variation in phenylalanine), proved to have defective biopterin metabolism.

The most useful investigations for confirmation or exclusion of defective biopterin metabolism depended upon whether the initial plasma biopterin was 'high' or 'low'. In the patients with 'high' values measurement of dihydropteridine reductase activity, with repeat plasma biopterin measurement when phenylalanine had fallen to the normal range, enabled a firm diagnosis of dihydropteridine reductase deficiency to be made. In the presence of 'low' initial biopterins urine pterin analysis indicated a partial block in the conversion of neopterin to biopterin. This patient died before an oral load of tetrahydrobiopterin could be given, and the possibility that biopterin deficiency was due to profound malnutrition, rather than to an inborn error, cannot be excluded. The effects of disturbed biopterin metabolism on central dopamine and serotonin synthesis can be assessed by measurement of homovanillic and 5-hydroxyindolacetic acids in CSF. Although it was not performed here, it is also useful to measure the noradrenaline metabolite 3-methoxy 4-hydroxyphenylglycol.

In the patient with dihydropteridine reductase deficiency tetrahydrobiopterin in a single dose of 7·5 mg/kg, or a daily dose of 20 mg/kg, failed to control neurological symptoms or improve neurotransmitter amine synthesis and also failed to raise the already high CSF total biopterin concentration. These findings contrast with those reported in a study of a patient with defective synthesis of biopterins in whom it was possible to raise CSF biopterins by oral treatment with tetrahydrobiopterin,[21] and another study showing that symptoms could be controlled in a patient with a synthesis defect.[13]

For the first 18 months of treatment our patient with dihydropteridine reductase deficiency made good progress on neurotransmitter replacement therapy, first in combination with a low phenylalanine diet, later with 50 mg/day tetrahydrobiopterin. Unfortunately, as in a similar patient described previously,[22] progress during the third year of life was less satisfactory, with evidence of neurological deterioration due to a secondary defect of folate metabolism.[17]

In 50 children with neurological disease and without hyperphenylalaninaemia plasma biopterin concentrations were similar to those of healthy children,[6] suggesting that in patients with normal phenylalanine concentrations general disturbance of biopterin metabolism is rarely the cause of progressive intellectual loss or extrapyramidal disturbance. CSF biopterin concentrations in children without movement disorder and children with torsion dystonia were similar to those in children with leukaemia (4·2 ng/ml) studied before treatment (unpublished data). CSF biopterin concentrations were lower in children with movement disorder other than torsion dystonia, a finding which can best be explained as due to anatomical or functional abnormality of the brain areas normally contributing to CSF biopterin rather than as the result of a primary defect of biopterin metabolism.

Six adult patients with Huntington's chorea also had normal plasma biopterin and low CSF total biopterin concentrations (1·9 ng/ml) (unpublished observations). A study of 'hydroxylase cofactor activity' in CSF found concentrations equivalent to 20 μmol/l tetrahydrobiopterin (4·2 ng/ml) in adult controls, and patients with movement disorder (Parkinson's disease and Huntington's chorea) again showed a reduction of 50% or more.[8]

Profoundly low CSF 'hydroxylase cofactor activity' has been reported in several members of two families with torsion dystonia.[9] These patients did not manifest the degree of neurological disturbance that might have been expected[2] if tetrahydrobiopterin in the central nervous system had indeed been severely reduced. These results contrast with the normal crithidia results in the patients with torsion dystonia described here, although one in whom amine metabolite concentrations were measured did show reduced concentrations of dopamine and serotonin metabolites in the CSF, suggesting that interference with tyrosine and tryptophan hydroxylation might have been present. We speculate that an inhibitor of the aromatic hydroxylases is present in the CSF and brains of some patients with torsion dystonia, which, without direct interference in biopterin synthesis, reduces 'hydroxylase cofactor activity' and amine turnover. The association reported here of achalasia of the cardia with torsion dystonia and a disturbance of amine metabolism is of interest as the pathogenesis of both disorders remains a mystery.

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Nasogastric compared with nasoduodenal feeding in low birthweight infants

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SUMMARY One hundred successive infants weighing less than 1500 g at birth were allocated alternately to intermittent nasogastric or continuous nasoduodenal feeding regimens. Eighty were appropriate for gestational age, and of these 25 fed successfully by nasogastric tube and 16 tolerated nasoduodenal feeding until 1600 g. No significant differences in either calorie intake or growth rates were identified throughout the seven weeks of the study. Because of the increased complexity and radiological exposure involved with feeding transpylorically, nasogastric feeding may be preferred as a method of feeding the low birthweight infant.

The very low birthweight infant requires a protein and calorie input sufficient to sustain growth and brain development.[1 2] Parenteral nutrition has been widely used to achieve this goal,[3] but the risks of cholestasis and sepsis[4 5] associated with this method have caused renewed interest in enteral feeding. Concern about mild aspiration associated with nasogastric feeding of the preterm infant[6] has encouraged the use of transpyloric routes—both nasoduodenal and nasojejunal—but studies do not concur over which method carries better growth rates and fewer complications.[7–9]

The present study compares two groups of infants of birthweight less than 1500 g. In one group feeding was by nasogastric tube, while the other group was fed initially by the nasoduodenal route.

Patients and methods

Between September 1982 and February 1984 all infants of birthweight 750 to 1500 g admitted to the Neonatal Intensive Care Unit, Simpson Memorial Maternity Pavilion, Edinburgh, within 24 hours of birth were entered into the study. All 100 infants were allocated alternately to nasogastric or nasoduodenal feeding regimen on a rigidly observed basis uninfluenced by the clinical condition of the infant. On completion of the trial infants appropriate for gestational age (between 10th and 90th centiles)[10] were selected from both groups for comparison of outcome.

Fluid intake targets were the same. Soon after birth a peripheral intravenous infusion was started based on a 9·5% dextrose cocktail with sodium content 2 mmol/100 ml. No amino acid nor lipid solutions were given. At three hours a feeding tube was passed and, if positioned successfully, milk feeds began at 0·5 ml/hour (for infants of birthweight less than 1000 g at birth) or 1 ml/hour (for infants of birthweight between 1000 and 1500 g). Similarly, six hourly increments of milk intake were by 0·5 ml/hour or 1 ml/hour according to weight. Planned fluid requirements in both nasogastric and transpyloric groups began at 50 ml/kg/day on day one, and increased by 25 ml/kg/day to 150 ml/kg/day. Decisions to increase still further were taken on an individual clinical basis.

In the group fed nasogastrically a 5 gauge (Argyle) feeding tube was passed at three hours and the position checked by acid reaction of the aspirate with litmus paper. Hourly bolus feeds were given by syringe administration. In the group fed transpylorically initial passage of a 5 FC silastic nasoduodenal tube (Vygon) was attempted at three hours of life, and continuous feeding was begun when the tube was in position, which was confirmed radiologically. The optimum tube end site used was the second part of the duodenum. Primary failure of passage was defined as inability to pass a tube through the pylorus on any occasion. In some infants, previously intubated successfully, the tube became displaced: subsequent failure to reposition the transpyloric tube was termed secondary failure. In both groups intravenous dextrose electrolyte solution supplemented the infants' planned fluid requirements until full enteral feeding was established. At 1600 g both groups were fed by intermittent hourly nasogastric feeding, progressing to two hourly feeds at 1750 g weight, three hourly feeds at 1800 g, and thereafter full bottle or breast feeding on an individual basis.

Infants were weighed naked on admission and then daily until discharge using an integrated electronic balance (Mettler 515). Crown-rump and crown-heel lengths were measured weekly using a Harpenden neonatometer, and occipitofrontal circumference was also documented on a weekly basis. Mortality and number of outborn versus inborn infants were compared by 2×4 contingency tables. All other statistical analysis was by Student's t test.

Results

Of the 50 infants allocated to the primarily nasogastric regimen, 35 were appropriate for gestational age, while 45 were appropriate for gestational age in the nasoduodenal group. Table 1 shows that there were no significant differences between the groups in sex, birthweight, crown-heel length, and occipitofrontal circumference. The original transpyloric group seemed to be of an earlier gestation and smaller crown-rump length ($p=0·05$). The proportion of inborn to outborn infants was similar in both groups, nine of the inborn infants being fed nasogastrically having been transferred in utero from other hospitals, while 14 of the inborn infants being fed transpylorically were similarly antenatal transfers (not significant). The original transpyloric group had significantly poorer Apgar scores at one and five minutes.

Table 2 shows that of the 35 infants appropriate for gestational age fed nasogastrically, six died. Five of these had massive intraventricular haemorrhage, and the sixth was severely birth asphyxiated. Four of the infants originally fed nasogastrically developed necrotising enterocolitis, which was treated successfully by total parenteral nutrition and intravenous penicillin, gentamicin, and metronidazole. Of the 45 infants appropriate for gestational age allocated to transpyloric feeding, 21 died, 16 of whom had an intraventricular haemorrhage, three of whom were severely asphyxiated but postmortem permission was refused, one who was of 24 weeks' gestation, and one who died of bronchopulmonary dysplasia. Table 2 also shows that 13 of the original nasoduodenal group failed to tolerate nasoduodenal

Table 1 *Characteristics of infants appropriate for gestational age at birth. Values are mean (SD)*

	Nasogastric group	*Original transpyloric group*	*p value*
No of infants	35	45	
Boys/girls	23/12	32/13	NS
Birthweight (g)	1223 (229)	1132 (213)	NS
Gestation weeks	28·5 (2·0)	27·7 (1·6)	0·05
Crown-rump length (cm)	25·9 (1·5)	25·2 (1·6)	0·05
Crown-heel length (cm)	38·7 (2·5)	37·9 (3·1)	NS
Occipitofrontal circumference on third postnatal day (cm)	26·9 (1·7)	26·1 (2·0)	NS
Inborn/outborn	31/4	36/9	NS
Apgar score at: one minute	6·2 (2·7)	3·6 (2·6)	<0·001
five minutes	8·3 (1·5)	6·3 (2·4)	<0·001

Table 2 *Outcome (No of infants) of feeding methods of infants appropriate for gestational age*

	Feeding method		
	Nasogastric	*Nasoduodenal*	*p value*
No of infants	35	45	
Successful feeding to 1600 g	25	16	
Total no of deaths	6	21	<0·01
No of deaths before tube passage attempted	2	10	
Failure of method	4	13	
Cause of failure of method:			
Necrotising enterocolitis	4	0	
Therapeutic use of pancuronium	0	6	
Primary failure of tube passage	0	1	
Secondary failure of tube passage	0	3	
Recurrent misplacement	0	1	
Bile vomits	0	2	
Hazards:			
X ray films for tube positioning mean (SD)	0	10·6 (7·9)	

feeding. Six had severe respiratory distress, tolerated ventilation poorly, and required to be paralysed: five of these subsequently died, but the other was fed successfully by nasogastric tube four days later. No infant developed necrotising enterocolitis while a nasoduodenal tube was in place, although one of the transpyloric group, after secondary failure of passage of the nasoduodenal tube, was switched to nasogastric feeding, and necrotising enterocolitis was diagnosed three days later. The increased radiological exposure of the 34 infants who had successful passage of at least one nasoduodenal tube is shown.

Twenty five infants were fed successfully by nasogastric tube until 1600 g, and 16 of the original transpyloric group also achieved this weight by the nasoduodenal route. Table 3 shows that these two groups were similar in all variables measured. In addition, as is shown in Table 4, no differences in growth velocities were identified between the two groups. Furthermore, no differences between the two successful groups were shown when mean daily fluid and calorie intakes were compared for each of the first seven postnatal weeks. The mean rate of displacement of nasoduodenal tube into stomach was 13 times for these 16 infants.

Table 3 *Details of infants appropriate for gestational age fed successfully to 1600 g. Values are mean (SD)*

	Feeding method	
	Nasogastric	*Nasoduodenal*
No of infants	25	16
Boys/girls (no)	18/7	11/5
Outborn/inborn (no)	2/23	4/12
Gestation weeks	28·9 (2·1)	28·8 (1·5)
Birthweight (g)	1259 (199)	1303 (140)
Crown-rump length at birth (cm)	25·9 (1·4)	25·9 (1·3)
Crown-heel length at birth (cm)	38·9 (2·3)	39·1 (1·9)
Occipitofrontal circumference at birth (cm)	27·2 (1·6)	27·2 (1·6)

p=NS for all values.

Table 4 *Growth variables of infants appropriate for gestational age successfully fed to 1600 g. Values are mean (SD)*

	Feeding method	
	Nasogastric	*Nasoduodenal*
No of infants	25	16
Postnatal weight loss (%)	14·6 (5·4)	17·5 (4·6)
Day of maximal postnatal weight loss	5·2 (2·3)	5·4 (2·2)
Day to regain birthweight	15·9 (5·1)	16·6 (5·9)
Day to achieve 1600 g	29·8 (11·5)	28·6 (8·6)
Growth of occipitofrontal circumference (cm/week)	0·8 (0·3)	0·8 (0·4)
Growth of crown-rump length (cm/week)	0·6 (0·7)	0·7 (0·3)
Growth of crown-heel length (cm/week)	0·8 (0·2)	0·7 (0·4)

p=NS for all values.
Growth velocities are calculated over the first six weeks of life.

Discussion

In this study 100 successive infants of birthweight less than 1500 g were allocated alternately to initial nasoduodenal or nasogastric regimens independent of their clinical condition at birth. However, highly significant differences in Apgar scores at one and five minutes were obtained by attending staff who were generally unaware to which method of feeding the infant would be allocated. This chance occurrence may largely account for the greater mortality in the group fed nasoduodenally.

Poor weight gain of infants fed nasojejunally has been described,[7] [9] but a nasoduodenal approach has been claimed to be more physiological and to carry a lower risk of complications.[6] In our 41 infants appropriate for gestational age who fed successfully to 1600 g by the routes originally allocated no significant differences in growth rates were identified, an observation in keeping with the findings of Pereira and Lemons.[8]

Concern has been expressed about the association between transpyloric feeding and the development of necrotising enterocolitis and perforation.[11] [12] Necrotising enterocolitis can occur with nasogastric feeding, however,[13] and all five infants with this disorder in the present study were being fed nasogastrically at the time of diagnosis. No episode of aspiration of milk was identified in any of the original 100 very low birthweight infants and no child fed nasogastrically required to be changed to the transpyloric regimen.

Thirteen of the infants allocated to the original transpyloric regimen did not tolerate it. In one child the tube failed to pass in seven attempts over 36 hours. Three infants were successfully transpylorically intubated, but the technique failed thereafter when a further tube was required. One infant was recurrently intubated without difficulty, but on eight occasions in fours days the tube tip fell back from the second part of the duodenum into the stomach, resulting in poor weight gain because of recurrent method failure. Two infants had frequent bile vomits on two successive days, and, although no aspiration of vomit was identified, the feeding method was changed to nasogastric, and the problem promptly resolved. The high rate of displacement of nasoduodenal tube into stomach (mean 13 times) compares poorly with results previously achieved in our unit (mean 2·7 times) using the third part of the duodenum as the optimal endtube site.[5]

While the tip of a transpyloric tube can be positioned by ultrasound techniques, in many units *x* ray films are used for this purpose. The mean of 10·6 *x* ray films required in our study specifically for siting the nasoduodenal tube is recognised as a disadvantage of the method. One attempted passage of a nasoduodenal tube resulted in intubation of the right main bronchus: this was identified radiologically, no milk was administered, the tube was removed, and the infant remained asymptomatic.

In the present study the group that tolerated nasoduodenal feeding showed no benefits in either fluid and calorie intake or growth rate when compared with the infants given intermittent nasogastric feeds. Furthermore, the nasoduodenal method is of greater complexity and in many centres requires an *x* ray film to confirm end tube site. Intermittent nasogastric feeding should be considered as a suitable method of feeding low birthweight infants.

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Norwalk like viruses: study of an outbreak

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SUMMARY An outbreak of acute non-bacterial gastroenteritis is reported, during which a ward had to be closed, and stool samples from 15 patients showed a virus structurally similar to the Norwalk agent.

The Norwalk agent derives its name from an outbreak of acute non-bacterial gastroenteritis that occurred in Norwalk, Ohio, in 1968.[1] Subsequent transmission of stool filtrates free of bacteria to adult volunteers showed that the symptoms could be reproduced,[2] and immune electron microscopy showed 27 nm particles.[3] Even without antibody these particles aggregate and have a fuzzy edge, thought to represent a surface substructure, which is beyond the limit of resolution of the electron microscope to define further. Particles with a similar appearance have been called Norwalk like viruses.[4] An experienced microscopist can distinguish such particles from other small round viruses seen in stool preparations: these include astrovirus, calicivirus,[5] and small round featureless viruses.[6] There are at least three antigenically distinct viruses in the Norwalk like group,[7] and the exact serotype can be determined only by immune electron microscopy using antibody from infected individuals. Such antibody is not generally available in this country, so the agents in our study could be classified only on morphological grounds. The Norwalk like viruses are thought to be ribonucleic acid viruses of calicivirus type.[8]

Norwalk like viruses, in contradistinction to rotaviruses, are regarded in the United States of America as primarily pathogens of older children and adults.[9] In developed countries serum antibody is acquired chiefly during adolescence, whereas in Bangladesh 100% of children have been found to acquire antibody by the age of 4 years.[10] The population served by our hospital could be seen as a mixture of these two extremes. Acquisition of antibody does not protect against the disease and in fact is associated with recurrent infections by the same serotype of Norwalk virus.[11] Thus infants are not likely to be protected by maternal antibody.

The illness produced by Norwalk like viruses is generally mild, lasting one to two days, with a variety of symptoms, including nausea, vomiting, diarrhoea, malaise, fatigue, headache, and low grade fever. The incubation period is generally one to two days,[4] but may be up to three days.[12] Transmission may be by the faeco-oral route, but may also be through vomit, which may be aerosolised, and so cause airborne transmission.[13]

Methods

Patients on the open ward were nursed with standard handwashing precautions between patients, while those in cubicles were nursed with the extra precautions of gloves, plastic aprons, and gowns.

Samples of stool were collected whenever a diarrhoeal illness was suspected, usually because of

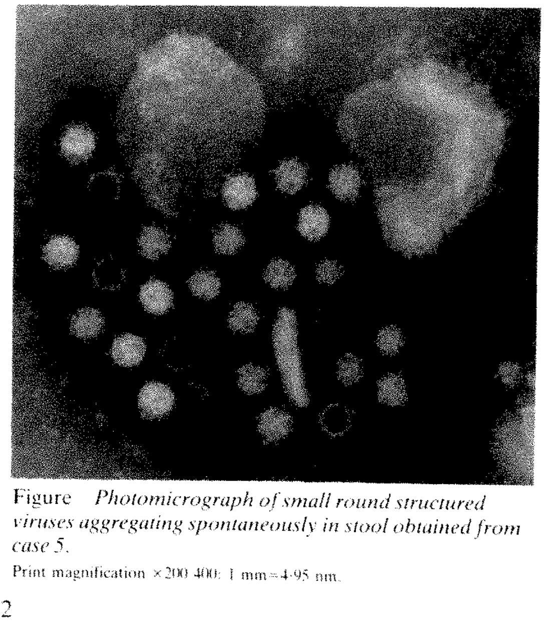
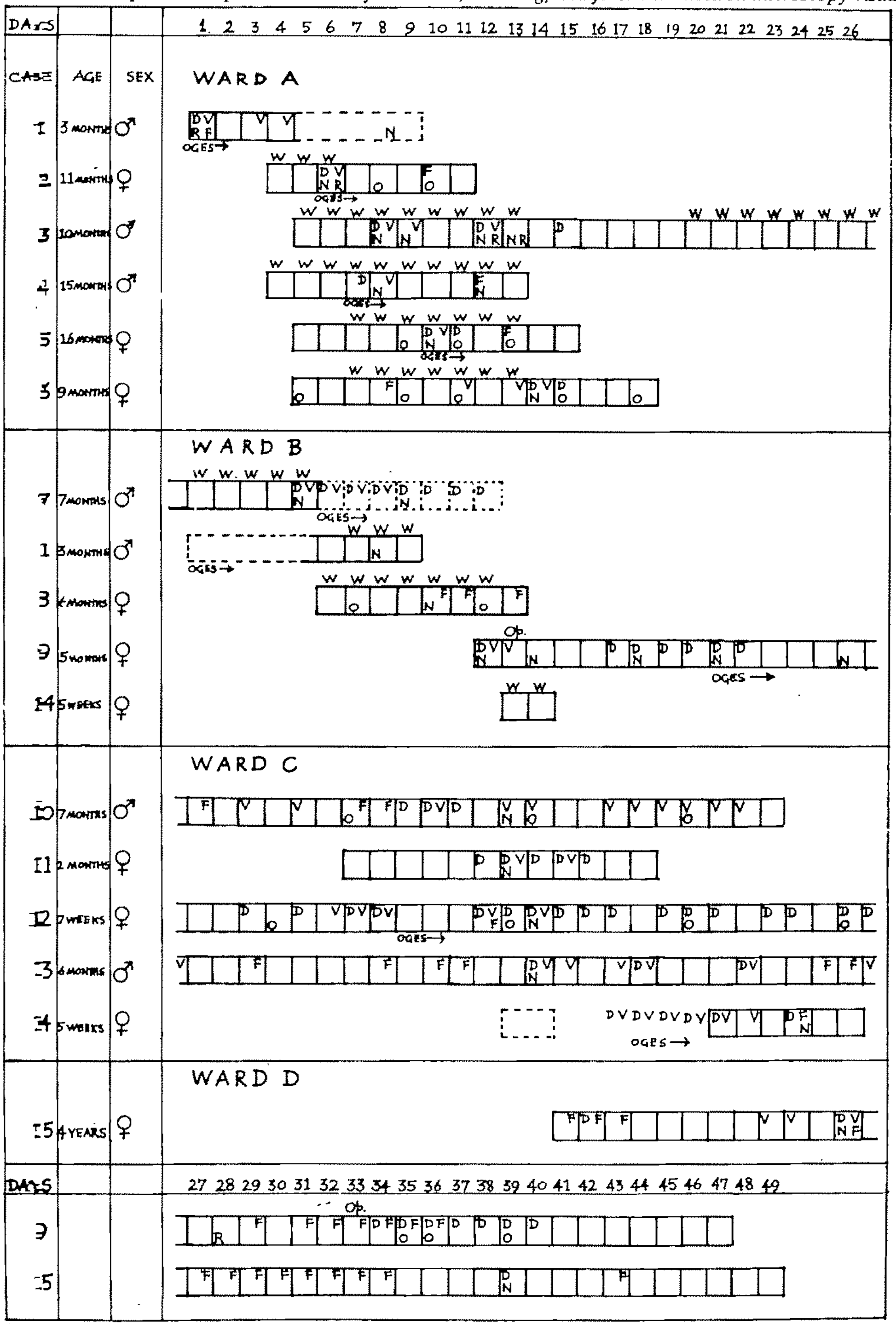


Figure *Photomicrograph of small round structured viruses aggregating spontaneously in stool obtained from case 5.*

Print magnification ×200 400; 1 mm=4·95 nm.

Table 1 *Temporal and spatial relations of diarrhoea, vomiting, and fever with electron microscopy visualisation of virus*



D=Diarrhoea, construed as a significant increase in the frequency of looseness of stools.
V=Vomiting (not regurgitation).
F=Fever of 37·5°C or more (axillary).
W=above a box means that the patient was in the open ward for all or part of that day. Unmarked boxes indicate that the patient was nursed in a cubicle.
N=Small round structured viruses of Norwalk virus type seen in stool passed on this day.
R=Rotavirus seen in stool passed on this day.
O=Electron microscopy of stool passed on this day disclosed no virus.
OGES=Oral glucose electrolyte solution started on this day.
Op=Surgery under general anaesthesia on this day; nil by mouth for a time afterwards.

Table 2 *Clinical details of patients, in chronological order of occurrence of small round structured viruses in the stool. The numbering of the days refers to Table 1*

Case 7—Diaphragmatic hernia repaired at birth. Admitted four days before day 1 for treatment of a chest infection on the open ward. He developed diarrhoea and vomiting on day 5, and a stool specimen was sent on the first day of symptoms. Small round structured viruses were seen the same day, and he was transferred the following morning to the hospital's isolation ward, according to surgical ward policy. His symptoms gradually settled on treatment with oral glucose electrolyte solution: he required two regrades, and had small round structured viruses in his stool again on day 9.

Case 2—Admitted with suspected non-accidental injury to the open ward (day 4). She developed diarrhoea and vomiting on day 6, and was put into a cubicle on the same day. She responded rapidly to oral glucose electrolyte solution despite having a dual infection.

Case 1—Pyloromyotomy and Ladd's procedure at 3 weeks of age. He was admitted on day 1 with a 24 hour history of diarrhoea and vomiting. He was febrile and drowsy. Cerebrospinal fluid, chest *x* ray film, and blood cultures showed no infection, but rotavirus was seen in the first day's stool. He responded very rapidly to oral glucose electrolyte solution, but he then developed bile stained vomiting, and *x* ray films showed the 'double-bubble' appearance of duodenal obstruction. He improved after being taken over by his surgical team on day 4, with nasogastric suction and intravenous fluids, followed by gradual reintroduction of normal diet. He was transferred to the surgical ward (B) on day 5. He did not pass a stool for four days and was therefore moved out of his cubicle before small round structured viruses were seen in the first stool he had passed (day 8) since his episode of obstruction. He was then rapidly discharged.

Case 3—Second admission with atopic eczema and failure to thrive. He was admitted on this occasion for topical treatment and a diet of 'Nutramigen' only. He seemed to develop two distinct episodes of symptomatic infection, the first single and the second dual. Neither made him ill, but they both interfered with his weight gain.

Case 4—Admitted for investigation of failure to thrive, which was found to be due to housing problems.

Case 5—Cows' milk protein intolerance. She was admitted for a jejunal biopsy, to be followed by lactose challenge and then milk challenge. The lactose challenge had to be abandoned because of symptoms related to brief carriage of Norwalk like virus.

Case 8—Congenital anorectal atresia and renal anomalies. The former had been treated by colostomy, which made it impossible to judge from the nursing records whether she had had diarrhoea. She had had meningitis aged 3 weeks, with hydrocephalus and seizures as sequelae. She was admitted on this occasion for control of fits. Samples were sent because of her proximity to case 7. She had a mild febrile illness associated with brief passage of small round structured viruses.

Case 9—Spina bifida and hydrocephalus, treated surgically soon after birth. She was transferred from her local hospital because of a cerebrospinal fluid leak, and was noted before transfer to be passing loose stools, so was put straight into a cubicle. Her admission (day 12) specimen contained small round structured viruses, as did subsequent specimens up to day 26. There was little correlation between viral carriage and symptoms noted at the time, but she did have a prolonged period of diarrhoea, attributable to the viruses, which settled on treatment with oral glucose electrolyte solution started on day 21. She subsequently developed rotavirus. Her initial vomiting was thought possibly to be due to raised intracranial pressure, and a prolonged fever was attributed to problems with her shunt. A second period of diarrhoea could not be associated with a virus. Her medical problems do not provide an explanation for the apparently prolonged carriage of Norwalk like viruses—but these may have comprised more than one strain.

Case 10—Admitted 44 days before day 1. He had subtotal villous atrophy of uncertain cause, which responded to treatment with 'Alfaré' formula feed; pelviureteric junction obstruction; and transient abnormalities of T cell function. His immunity was normal at the time of this infection. His symptoms show no clear relation to carriage of small round structured viruses.

Case 11—Bronchiolitis. She had a brief episode of gastroenteritis clearly associated with carriage of small round structured viruses, but not severe enough to require treatment with oral glucose electrolyte solution.

Case 6—Failure to thrive. On admission to the ward (day 5) she was put in the cubicle vacated by case 1. On day 7 she was moved out of a cubicle and was put back in when the ward was reopened on day 13. Only one of a number of stools was seen to have small round structured viruses, and she had mild symptoms over an eight day period, at least some of which could be attributed to this.

Case 12—Admitted eight days before day 1, with pertussis. She had frequent episodes of vomiting with coughing spasms, so 'V' was entered in Table 1 only if this seemed to be more than usual. She also seemed to have frequent loose stools, which settled on the one occasion when oral glucose electrolyte solution was given, but did not bear a very clear relation to carriage of virus (she was discharged on day 29).

Case 13—Panhypopituitarism due to congenital toxoplasmosis. He was admitted with hypernatraemia nine days before day 1; some of his vomiting may have been related to electrolyte or cortisol imbalance. He did, however, have mild diarrhoea and vomiting associated with carriage of small round structured viruses, and this may possibly have contributed to problems adjusting the dosage of his replacement hormones (he was discharged on day 47).

Case 14—Elective hernia repair on ward B. She developed gastroenteritis three days after discharge and was treated as an outpatient in casualty because of a shortage of cubicles. After a poor response to treatment with oral glucose electrolyte solution, she was admitted to ward C, where her symptoms settled.

Case 15—T cell acute lymphoblastic leukaemia. She was receiving intensive induction chemotherapy. A prolonged fever was thoroughly investigated, and the only identifiable cause found was a Norwalk like virus, whose stool carriage seemed also to be prolonged. Her neutrophil count was negligible until day 34, and did not begin to approach safe levels until day 45—much later than envisaged in the treatment protocol, which therefore had to be adjusted. This was blamed at the time on the virus.

one or more loose stools, as a follow up on patients already found to be excreting Norwalk like virus, and on some contacts of infected patients. The samples were sent for light microscopy, bacterial culture, and electron microscopy (performed by DL), according to ward policy, with the follow up and contact specimens being sent for electron microscopy only. Stool was not routinely cultured for viruses (Norwalk like viruses cannot be isolated in viral culture at present). Specimens of vomit were not, unfortunately, sent for electron microscopy.

Stools were prepared as 30% suspensions in distilled water and examined by a direct electron microscopy method.[14] Some were stored at −20°C before examination. All the viral particles observed from the outbreak and classified as small round structured viruses of Norwalk type had a similar morphology, with an indistinct substructure, a fuzzy edge, and an approximate diameter of 30 nm (Figure).

Results

Table 1 shows the temporal and spatial relations of diarrhoea, vomiting, and fever with electron microscopy visualisation of virus. Each box represents a day during admission. The 15 patients were those found to have Norwalk like virus in stool specimens sent during a 26 day period. This period was chosen to include all possible links to the apparent outbreak. No other patients in the hospital were known to have small round structured viruses during these 26 days. The key explains the symbols used. Ward B is a surgical ward, the others medical. Potentially relevant details were extracted retrospectively from routine medical notes and nursing charts. Table 1 shows also when patients were in cubicles and when on the open ward. Two of the patients had apparently prolonged carriage and so are the subjects of a continuation of the Table beyond the arbitrary day 26.

Table 2 gives the reasons for admission and additional clinical details of the patients.

No child became significantly dehydrated in association with small round structured viruses. Nine children were treated with oral glucose electrolyte solution, and only case 1 required additional treatment for gastroenteritis. He required intravenous fluids at the time of rotavirus excretion, and again at the time of duodenal obstruction, which was interpreted as a complication of his previous surgery, albeit in retrospect associated with infection by Norwalk like virus. Patient 15 required intravenous fluids as part of her chemotherapy for leukaemia.

Ward A had the most pronounced spatial and temporal clustering of cases. Several nurses, the ward teacher, and a physiotherapist also became ill. No doctor admitted to having relevant symptoms. Samples were unfortunately not received from any of these adults. On all specimens sent bacterial cultures were negative for salmonella, shigella, enteropathogenic *Escherichia coli*, campylobacter, and aeromonas species, as was light microscopy for ova, cysts, and parasites, including cryptosporidia.

When it became clear, on day 8, that the number of free cubicles in the hospital would not be sufficient for the number of patients with loose stools, ward A was closed to admissions, and treated as one large cubicle. Patients were sent home when possible, or regarded as non-infectious when at least one stool specimen had no small round structured viruses on electron microscopy. When the number of patients giving rise to doubt had been sufficiently reduced (day 13) these were transferred to individual cubicles, and the ward was reopened.

The clinical picture of disease attributable to Norwalk like virus in this study is generally mild. In most children, it caused a brief episode of gastroenteritis; in a few of these the purpose of admission was compromised (cases 3, 4, 5, and 6). In some with pre-existent disease it seemed to contribute to complications (case 1). Combined virus infections including Norwalk like virus have been reported to cause more severe symptoms than Norwalk like virus alone,[15] and this may have contributed to the clinical picture in case 1, but seems to be of no relevance to cases 2, 3, or 9.

Because of the method of ascertainment of cases there is clearly a bias towards the correlation of gut symptoms with carriage of small round structured viruses. The relation is nevertheless tenuous in some cases (cases 8, 9, 10, and 12), suggesting that asymptomatic infection may occur more commonly than we have been able to show.

Discussion

Because the data are retrospective many unanswered questions remain. The initial impression of an 'outbreak' came not only from the number of patients with symptoms of gastroenteritis on the ward at once, but also from the number of staff who became ill.

Even when a stool sample is sent at the time of peak excretion of virus, electron microscopy is almost certainly not as sensitive at detecting small round structured viruses as at diagnosing rotavirus infection. Allowing in addition for incomplete sending of samples, there must have been significant under ascertainment.

Identification of the pattern of spread is made highly speculative by the numerous possible modes of transmission. Asymptomatic carriage enables faeco-oral transmission to take strange routes. Aerosol inhalation seems to occur,[13] and adult staff may, as with other viral infections, transfer the virus in respiratory droplets. The virus must have quite a high prevalence in the community to account for cases occurring in our hospital all the year round. Visiting adults and children may therefore transmit the organism to inpatients. Also contamination of surfaces is possible in spite of routine cleaning and disinfection procedures and may have been a further source of infection.

We had no way of distinguishing serotypes: two or more[7] may have been involved, and the patients with apparently prolonged carriage (cases 9 and 15) may actually have been reinfected with a different strain, as has been described with rotavirus.[16]

As no overlap in medical or nursing staff could be found between cases 7 and 2, nor any proximity of address, it was considered that case 1 must be the link between wards A and B, which was why he was put first in Table 1. He shared surgical staff with case 7, even before he moved wards, which might explain a transmission, through vomit, that would otherwise be backwards in time. There are, of course, alternative explanations for the simultaneous occurrence of cases on the two wards: it might even have been coincidence.

Case 2 developed a dual infection after two asymptomatic days on the ward. Although she was possibly incubating both the infections during these two days, the evidence seems more in favour of the hypothesis that she acquired them from case 1, despite his being in a cubicle at the time.

The subsequent cases on ward A are unlikely to have been coincidental, although case 9 on ward B probably was.

The four patients in cubicles on ward C in whom small round structured viruses were detected within a two day period are very suggestive of a common source. This was thought at the time to be the house physician involved directly with the care of cases 6, 10, and 11, and indirectly with the care of cases 5, 12, and 13. He apparently had no symptoms.

Infection with Norwalk like virus was originally thought to be a winter disease,[1] but outbreaks have occurred at all times of year.[8] In a previous study at this hospital the peak incidence of Norwalk like infections—presumably acquired in the community, at least principally—was in March, April, and May.[15] The collection of cases we report here occurred at the end of January and during February (day 8=1 February).

Outbreaks of infection with Norwalk like viruses are common world wide. A review of 24 such outbreaks includes five common source epidemics, due to contaminated water or food, and 17 episodes in institutionalised communities.[8] A minority of the latter type have occurred in hospitals, including a psychogeriatric unit,[12] a maternity unit,[17] and a children's asthma research institute.[18] Patient to patient spread was shown to be associated with symptomatic excretion by nursing and medical staff.[12 18]

Conclusion

Nosocomial infection with Norwalk like viruses may well be commoner than is generally realised. With the benefit of electron microscopy identification on morphological grounds, we have shown that significant spread of infection, albeit causing a generally mild illness, seems to occur in spite of standard nursing procedures and even isolation precautions.

We thank Professor J A Walker-Smith for helpful advice and Mr J H Spender for the typography of Table 1.

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British Paediatric Association

Annual meetings

1986	15–19 April	York University
1987	7–11 April	York University
1988	12–16 April	York University

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Evolution of neonatal intensive care in a district general hospital

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SUMMARY Before 1975 in Blackburn in the Premature Baby Unit monitoring facilities were limited. Ambient oxygen monitoring, blood gas analysis, and ventilation were not being performed. Gradually, special care was introduced and from 1978–80 all babies requiring intensive care and long term ventilatory care were transferred to the Regional Neonatal Intensive Care Unit. Not all babies with incipient or established respiratory failure, however, could be accepted, and those declined had unfavourable outcomes. In 1981 local intensive and ventilatory care was begun, and since then the survival of all babies has improved considerably. Our early neonatal mortality and neonatal mortality have fallen below the regional levels. In a district general hospital it is possible to achieve survival figures comparable with those of a regional centre.

Several reports have drawn attention to deficiencies in standards of perinatal care in Britain and have recommended improvements.[1–5] Regional organisation of neonatal intensive care has been widely developed in this country, and some large districts have also developed intensive care facilities.[6] Some regional centres accept all low birthweight babies, whereas others accept mainly babies with respiratory failure.[7] One author in a leading article questions the advisability of providing intensive care in most special care units: 'A conventional special care unit cannot become an intensive care unit overnight by the purchase of one or two mechanical ventilators'.[8]

A service directed towards incipient or established respiratory failure has its limitations, for when sick neonates requiring mechanical ventilation cannot be accepted, then their outcome is unfavourable.[9] This report examines the parallel development of a district neonatal intensive care unit alongside the regional intensive care unit and evaluates the results of such a policy.

Patients and methods

Blackburn, Hyndburn, and Ribble Valley Health District covers an area of 305 square miles. The total estimated residential population in 1983 was 272 900. Consultant maternity and special care are provided at Queen's Park Hospital. There are three general practitioner maternity units six to 10 miles from the main unit.

There is one special care unit with 20 cots. In 1975 it was known as the Premature Baby Unit. Monitoring facilities were very limited. Intubation, continuous monitoring of apex, respirations, ambient oxygen concentration, and blood gas analysis were not carried out. The Unit, however, had a high occupancy, and our early neonatal mortality (deaths within the first week) and neonatal mortality (deaths in the first 28 days) were higher than the North West Region.

The initial priority was to provide special care, with basic nursing and medical care—for example, more efficient resuscitation, better monitoring of vital functions, ambient oxygen concentration, and temperature control—together with close biochemical monitoring and early feeding.

Although the Regional Intensive Care Unit at St Mary's Hospital, Manchester, was keen to assist district hospitals with ventilatory support, we were able to transfer only babies who were robust enough to survive locally without early ventilatory support. By 1978 special care was well established and in 1979 we were able to offer some intensive care but we were relying on the Regional Centre to provide long term ventilatory support. Also from 1978 onwards we were able to transfer babies weighing less than 1000 g. In 1979 ventilation was first introduced. In 1979 most babies were ventilated for less than 24 hours. This was given either as a temporary support before the regional flying squad arrived or as a last ditch effort when the baby had reached end stage respiratory failure.

By 1980 it became obvious to us that the Regional Centre could not accept all the babies requiring ventilatory care. Hence in 1981, with the appointment of a third paediatrician, we embarked on long term intensive care. Now the only indication for transfer to the Regional Centre is shortage of nursing staff, or when all four ventilators are in use. In utero transfer is only undertaken when the Unit is full, or there is a very unusual problem such as severe Rh disease. This is done after discussion with local paediatricians and the Regional Unit. Babies with major surgical conditions are all dealt with at the Regional Centre.

Results

The annual total births in the district has varied from 3715 in 1975 to 4005 in 1984. Of the 11 923 total births in 1982–84, 9·5% (1129) were below 2500 g (regional percentage 7·8) and 21·7% (2585) were to Asian mothers (regional percentage 12). In the years 1976 and 1977, while special care was being developed, only seven babies weighing more than 1000 g were transferred to the Regional Centre for ventilation, and none below 1000 g were transferred. From 1978–80, 46 babies were transferred, 12 of whom were below 1000 g. From 1981 onwards only an occasional baby has been transferred for the reasons already stated.

With the introduction of intensive care the workload of the Unit has increased several fold. In spite of this, the total number of admissions to the Unit has progressively fallen. In 1975 roughly 15% of all births were admitted to the Unit. The figure for 1984 was 6·3% (251). Figure 1 shows how the workload of the Unit has steadily increased. Initially, ventilation was provided only for terminal respiratory failure. But as our experience grew babies with deteriorating blood gases were ventilated without hesitation. The number of intravenous infusions increased as more peripheral veins were used for parenteral nutrition. The average length of stay went up from 8·6 days in 1977 to 16·3 days in 1984. This is due to the increased length of stay of very low birthweight babies. Now the average length of stay of babies weighing less than 1000 g is 104·6 days, of babies weighing 1000–1500 g is 51·8 days, and of babies weighing more than 2500 g is 5·2 days.

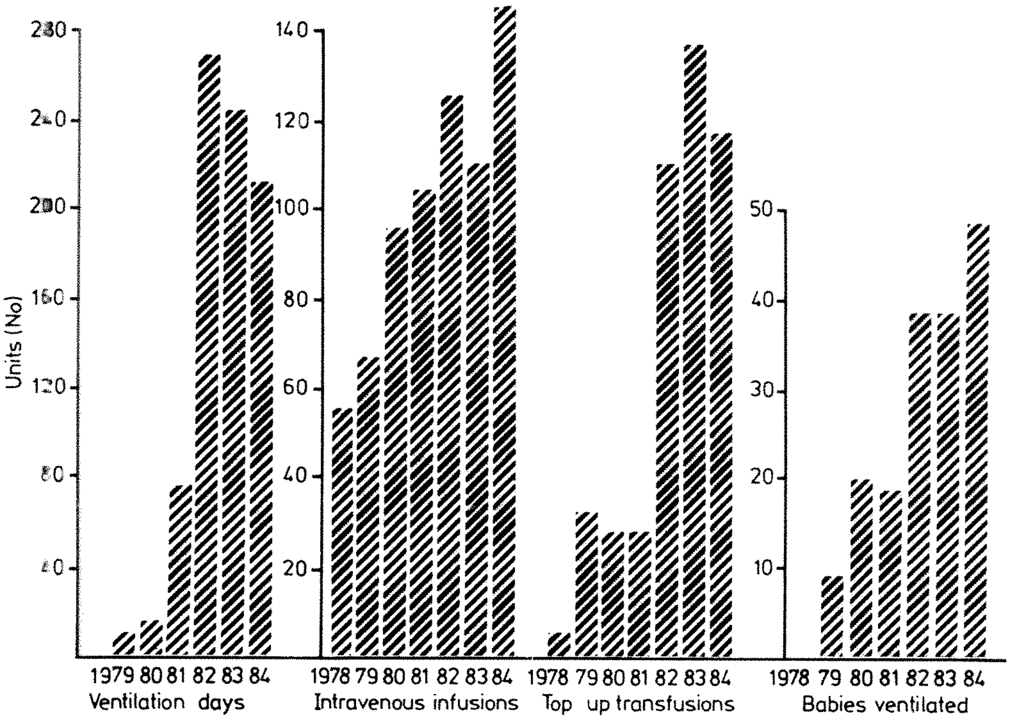

Fig. 1 *Distribution of the yearly workload in the Unit for the years 1978–84.*

Table 1 shows the percentage survival for ventilated babies of different weight groups. In 1979, 11 of our babies weighing greater than 1000 g were ventilated at the Regional Unit, of whom eight (73%) survived, whereas of the five babies ventilated locally only one (20%) survived. In 1981 (first year of local long term ventilatory care) our survival rate of all babies ventilated was similar to 1980 when most babies were transferred to the Regional Centre. Of the 56 babies over 1000 g ventilated locally for respiratory failure in the years 1983–84, 46 (82%) survived. With experience our survival rate for ventilated babies weighing less than 1000 g has improved considerably. The survival rate of babies weighing 1000 g or less transferred to Manchester was 33% (1979) and 25% (1980), and none of the babies ventilated locally survived until 1982 when the survival rate was 45% (11 babies). Of the 17 babies ventilated weighing 1000 g or less in the years 1983–84, 10 (59%) survived.

Ventilatory care is only one aspect of intensive care, and when the Unit is geared to providing intensive care in all its aspects the survival of all babies improves dramatically. Our survival rate of all babies weighing 750–1000 g was only 44% in 1978. In the years 1983–84 this had reached 78%, and the survival rate of babies weighing 1001–1500 g in 1983–84 was 87%. Although the workload of the staff has increased considerably in looking after very immature babies, this has not adversely affected the survival of larger babies (Table 2).

Our survival figures for babies weighing below 750 g remains poor (Table 2). Two babies below 750 g (both weighing 720 g) were ventilated in 1982, one for 55 days and the other for 58 days. To date both are developing normally except that one of them has sensory neural deafness, though her speech is normal. In 1984 a baby weighing 600 g was ventilated for 50 days. It is too early to predict her outcome.

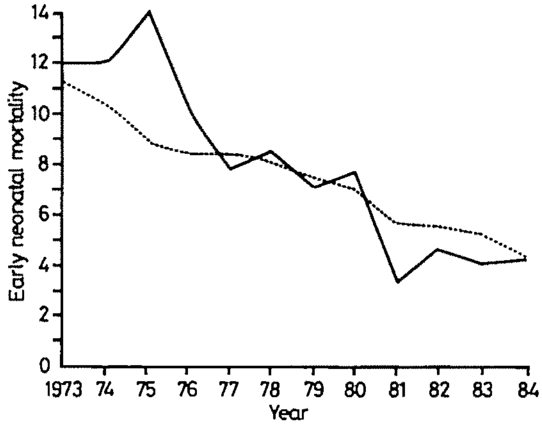

Fig. 2 *Comparison of early neonatal mortality in Blackburn District Hospital and the North West Region for the years 1973–84 (——=Blackburn; – – – – –=North West Region).*

Table 1 *Number (percentage) survival of ventilated babies, excluding those with lethal congenital malformations*

	All babies			*Babies weighing ≤1000 g*			*Babies weighing >1000 g*		
	RNICU	*Blackburn*	*Total*	*RNICU*	*Blackburn*	*Total*	*RNICU*	*Blackburn*	*Total*
1978	16 (50)	— —	16 (50)	5 (60)	— —	5 (60)	11 (45)	— —	11 (45)
1979	14 (64)	6 (17)	20 (50)	3 (33)	1 (0)	4 (25)	11 (73)	5 (20)	16 (56)
1980	16 (62)	7 (57)	23 (60)	4 (25)	1 (0)	5 (20)	12 (75)	6 (66)	18 (72)
1981	3 (67)	13 (61)	16 (62)	0 (0)	3 (0)	3 (0)	3 (66)	10 (80)	13 (77)
1982	3 (33)	13 (70)	36 (67)	0 (0)	11 (45)	11 (45)	3 (33)	22 (81)	25 (76)
1983	1 (100)	31 (77)	32 (78)	0 (0)	8 (62)	8 (62)	1 (100)	23 (83)	24 (83)
1984	0 (0)	42 (76)	42 (76)	0 (0)	9 (56)	9 (56)	0 (0)	33 (82)	33 (82)

RNICU=Blackburn babies transferred to Regional Necnatal Intensive Care Unit for ventilation.

Table 2 *Percentage survival of babies of various birthweights (values are total No of live births (% survival))*

	Weight groups (g)						
	<750	*750–1000*	*1001–1500*	*1501–2000*	*2001–2500*	*>2501*	*Total*
1975–76	— —	19 (15·8)	45 (60·0)	86 (76·7)	440 (96·1)	6690 (99·5)	7280
1977–78	1 (0)	16 (31·2)	31 (58·0)	114 (90·4)	401 (97·5)	6656 (99·7)	7219
1979–80	13 (0)	16 (43·8)	58 (79·3)	107 (93·5)	496 (98·8)	7269 (99·7)	7959
1981–82	11 (27·2)	14 (57·1)	47 (78·7)	117 (98·3)	479 (99·2)	7280 (99·8)	7948
1983–84	6 (16·7)	18 (77·7)	63 (87·3)	139 (95·0)	509 (99·0)	7124 (99·8)	7859

Our neonatal mortality in 1975 was 17 (North West Region 10·7). In 1983 it was 5·6 (North West Region 6·5), and in 1984 it was 5·4 (North West Region 5·3). Our early neonatal mortality in 1975 was 14 (North West Region 10·2). In 1983 it was 4·1 (North West Region 5·3), and in 1984 it was 4·3 (North West Region 4·4) (Fig. 2). Today, the commonest causes of our neonatal mortality are lethal congenital malformations (51·2%), babies weighing less than 1000 g (21%), and asphyxia (11·6%)

Discussion

Several reports have drawn attention to deficiencies in standards of perinatal care in Britain.[1-5] Very ill, low birthweight babies require a high standard of care with scrupulous attention to nursing and medical care. Regional intensive care units have been established in all regions, but the pattern of referral of these units varies. In the North West Region St Mary's Hospital, Manchester, provides a pattern of referral that is essentially crisis orientated and directed towards babies with incipient or established respiratory failure.[7] The demand for this service is increasing and many babies for whom transfer is required cannot be accommodated. The percentage of requests for transfer that were declined to individual hospitals ranged from 17–73%.[9] The neonatal survival of babies declined transfer compared unfavourably with the babies who were transferred.[9] During 1979–80 we found that if babies were declined transfer they not only stretched our resources but also that those babies that were offered long term ventilation did rather badly.

From 1981 long term ventilatory and intensive care has been provided locally. This was made possible by the establishment of an additional consultant paediatrician with experience in neonatal intensive care. Over the course of time the nursing staff establishment was increased. In 1975 there was only one sister in the Unit, but by 1984 this had been increased to nine. It was important for nurses to receive adequate training, and hence in 1977 a sister was seconded to a regional unit for the Joint Board for Clinical Nursing Studies Course 400 (now named 405). From then onwards each new sister appointed has been seconded to a regional unit for further training. By 1984 we had six sisters with such qualifications. The District Authority has accepted the importance of trained neonatal nurses and has funded all the secondments. Initially, the number of junior paediatric staff was small, but by 1980 we had two senior house officers wholly working with neonates. By 1981 we had two second on call senior house officers, and these with the registrar have provided one in three intermediate resident cover. The second on call also provides cover for general paediatrics.

Initial equipment for the Unit was provided by voluntary bodies, but the Health Authority has also provided equipment from the end of year unused money. We still rely heavily, however, on the generosity of local voluntary organisations who raise money for the Unit.

Babies can with efficient transport techniques receive care in the regional centre. The District Special Care Baby Unit can provide a good level of anticipatory care for high risk neonates. This requires a doctor with neonatal experience to be available at short notice (registrar or senior house officer). Facilities for monitoring heart rate, skin temperature, ambient oxygen concentrations, arterial blood gases, effective management of apnoea, and intervention before the baby deteriorates too far should now be available in all special care baby units, but this is no longer sufficient in some regions. Many referral units cannot accept all babies,[9] even though they may have established respiratory failure.

In Blackburn we have managed to progress from premature care in 1975 to long term intensive care within five years. Our survival rate of all babies ventilated has steadily improved from 60% in 1980 when most babies were transferred to the Regional Centre to 76% for all babies ventilated and 82% for babies ventilated weighing greater than 1000 g when all babies were ventilated locally. The most striking improvement has been in the survival of babies weighing 750–1000 g (survival rate 78%), 1001–1500 g (survival rate 87%) and 1501–2000 g (survival rate 95%), although this has not occurred at the expense of larger babies. The causes of neonatal death have altered, and now most babies die of lethal congenital malformations, extreme prematurity (weight below 1000 g), or asphyxia.

Greatly increased survival of immature babies, however, means increased facilities will be required outside the neonatal intensive care. Many of these babies will have readmissions, especially in the first year of life, to the children's ward. They also need careful developmental surveillance, including search for learning difficulties at school age.

Unless many subregional centres are to be established as recommended by the report of the House of Commons Social Services Committee on perinatal and neonatal mortality,[5] the only solution lies in encouraging large districts to carry out their own intensive care and relying on regional units to help out small units. This will encourage recruitment and improve the morale and training of staff employed in large district general hospitals. Close liaison with the regional unit and regular visits from regional neonatologists to the district hospital, however, is essential. In this respect we have been fortunate in establishing very close links with the regional centres and have had helpful criticisms in the management of our babies.

Besides the inability to accept all babies there are other disadvantages in regionalising intensive care. Parents have great difficulty in visiting babies at regional centres, both in terms of distance and expense. Low birthweight babies stay in the Intensive Care Unit for considerable periods. This has obvious implications for bonding and breast feeding.

We certainly agree with Congdon and Lelman that large districts can provide satisfactory intensive care for low birthweight babies.[6] The development of large regional intensive care units is not the only answer for all regions, as has been pointed out by the Maternity Services Advisory Committee.[10] The size, birth rate, and distribution of hospitals and their facilities differ among regions, and there is no one blue print for organisation of neonatal intensive care.

I thank Drs J W T Benson, M J Chiswick, and C Fossard for helpful criticism and Mrs M Robbins and Mrs M Hunt for their help.

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Immunoregulatory treatment for minimal change nephrotic syndrome

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SUMMARY Immunological studies were performed in 18 children with minimal change nephrotic syndrome proved by biopsy examination during relapse and in 15 age matched controls. All 18 children showed dysfunction of cell mediated immunity as evidenced by low absolute lymphocyte count, low blastogenesis index in response to phytohaemagglutinin stimulation, and reduced skin sensitivity to dinitrochlorobenzene when compared with controls. All 18 patients had low serum IgG concentrations, while the IgA, IgM, and C_3 concentrations in the serum were within normal limits.

Based on the evidence of depressed cell mediated immunity, 14 patients with nephrotic syndrome were treated with an immunoregulatory drug *l*-tetramisole (levamisole) for a period of 20–24 weeks. Six patients went into complete remission within 4–20 weeks of treatment, a further six patients went into partial remission, while two did not respond.

On follow up (six to 24 months after stopping levamisole), of the six patients who achieved complete remission, four continued to maintain the state and two relapsed after roughly six months. Of the six patients who achieved partial remission, two went into complete remission, two continued to be in partial remission, and two relapsed.

A variety of immunological alterations have been described in minimal change nephrotic syndrome.[1-3] Conventional treatment with steroids and immunosuppressants, although inducing a remission of the nephrotic state, increases the risk of severe life threatening infections in these children by further depressing the cell mediated immunity.

This study was undertaken to evaluate the immunological state of children with minimal change nephrotic syndrome in relapse who were not being given any immunosuppressive treatment and to assess the role of levamisole, an immunoregulatory drug, in the management of this disease in those who showed evidence of dysfunction in cell mediated immunity.

Patients and methods

Eighteen patients with nephrotic syndrome and 15 controls, all aged between 1 and 12 years, were studied.

All 18 patients had anasarca with proteinuria ≥ 40 mg/m^2/24 hours, hypoalbuminaemia $\leq 2 \cdot 5$ g/dl and hypercholesterolaemia ≥ 200 mg/dl. Histology of the renal biopsy specimen obtained percutaneously showed a minimal lesion in all 18 cases on light microscopy; the immunofluorescence was negative in all except one, which had faint deposits of IgM in mesangium.

The patients were further classified according to whether they had (a) single attacks, (b) infrequent relapses (<three a year), (c) frequent relapses (> two in six months or >three a year). None of them were receiving any immunosuppressants at the time of the study. Only two had earlier received cyclophosphamide, and that was more than two years before the present study. Immunological studies were undertaken on all these patients.

Tests for cell mediated immunity. These were (1) absolute T lymphocyte count by sheep red blood cell rosette formation; (2) blastogenesis by phytohaemagglutinin stimulation; and (3) skin testing for delayed hypersensitivity to neoantigen dinitrochlorobenzene.

Tests for humoral immunity. These were (1) absolute B lymphocyte count by rosette formation; and

(2) estimation of immunoglobulins IgG, IgM, and IgA in serum by electroimmunoassay (Rocket technique).

Complement system. Estimation of C_3 component in serum was by single radial immunodiffusion.

Treatment with levamisole. Fourteen patients were given levamisole (2·5 mg/kg body weight) as a single dose at bed time either daily or on alternate days for a period of 20–24 weeks. During this period they were observed clinically with special reference to weight, blood pressure, oedema, and the number and severity of infections. Laboratory monitoring was performed weekly by blood count and complete urinalysis and monthly for blood urea, serum creatinine, and 24 hours urinary albumin concentrations. Serum proteins and cholesterol were assessed at the end of treatment. Immunological studies were repeated when possible at the end of treatment. Response was termed as complete remission when the urine was free of albumin in three consecutive samples. Partial remission was when there was a reduction in proteinuria to + or ++ and the patient was free of oedema. No response was when there was no reduction in proteinuria. The patients were followed up for six months to two and a half years to assess their nephrotic state.

Results

There were 18 patients in relapse aged 1–12 years and 15 age matched controls. Tables 1 and 2 show the results of their immunological studies, respec-

Table 1 *Results of immunological study in 18 patients with minimal change nephrotic syndrome*

Case no	*Haemoglobin (g/l)*	*Serum albumin (g/dl)*	*Skin reactivity to dinitrochlorobenzene (grade)*	*Absolute mononuclear cell count (per mm^3)*	*T cell count (per mm^3)*	*B cell count (per mm^3)*	*Phytohaemagglutinin index at 72 hours*	*IgG (mg/dl)*	*IgA (mg/dl)*	*IgM (mg/dl)*
1	114	2·0	2	5587	1898	509	3·8	500	84	176
2	128	1·4	2	3696	1182	813	2·1	400	124	190
3	136	1·0	3	1440	648	403	1·8	640	94	129
4	97	0·8	0	3744	1835	973	1·2	520	80	146
5	88	0·6	2	3328	1265	765	3·8	340	92	138
6	118	2·1	2	4575	1007	685	3·6	528	74	260
7	114	2·2	0	1760	387	176	3·9	400	74	140
8	118	0·6	2	4312	1207	1035	2·8	580	68	120
9	100	1·8	2	3432	1304	309	6·2	840	114	138
10	132	0·9	1	5928	512	1363	3·0	480	84	180
11	112	0·6	0	2331	652	303	2·6	460	100	136
12	125	2·5	0	3432	1510	412	1·2	380	64	120
13	104	1·9	2	3808	1312	609	3·2	840	110	143
14	110	1·5	2	2430	1966	437	3·6	480	48	120
15	100	3·4	1	2343	1267	398	2·4	620	72	141
16	120	1·2	0	3393	1243	238	4·9	720	96	154
17	114	1·5	1	4012	1387	422	3·6	840	84	126
18	108	1·8	0	6574	1942	1052	3·4	800	102	134

Table 2 *Results of immunologicdl study in the 15 controls*

Case no	*Haemoglobin (g/l)*	*Serum albumin (g/dl)*	*Skin reactivity to dinitrochlorobenzene (grade)*	*Absolute mononuclear cell count (per mm^3)*	*T cell count (per mm^3)*	*B cell count (per mm^3)*	*Phytohaemagglutinin index at 72 hours*	*IgG (mg/dl)*	*IgA (mg/dl)*	*IgM (mg/dl)*
1	142	3·9	3	4800	3168	1056	5·8	1100	101	143
2	135	3·2	2	6200	4216	1426	6·6	830	94	186
3	110	4·0	4	2920	1119	525	7·4	1349	97	96
4	132	3·8	3	8000	5120	1120	4·4	1760	101	89
5	118	3·9	4	11000	6490	1540	10·8	1400	120	181
6	112	3·5	Negative	12000	7440	2320	6·4	620	97	128
7	116	3·6	3	3800	2242	646	4·5	622	180	201
8	113	4·1	4	4800	3168	672	3·9	934	190	190
9	118	3·7	3	3200	1888	480	6·9	1760	120	136
10	111	3·4	4	4200	2394	672	3·8	1100	120	97
11	133	3·9	3	4000	2320	720	6·8	688	160	81
12	128	3·6	4	4600	2714	644	3·9	948	138	201
13	122	3·7	4	3800	2808	608	9·4	1100	180	96
14	147	3·9	3	2400	1512	432	4·8	800	101	138
15	120	3·3	3	3600	2374	792	7·8	990	124	134

tively. The statistical analysis of these results are as follows.

The absolute T lymphocyte count in patients with nephrotic syndrome had a mean (SD) value of 1387 (52[illegible]). The mean (SD) value for the control group was 3265 (1808) (p<0·001) (Figure 1). The blastogenesis index to phytohaemagglutinin stimulation at 72 hours was 2·87 (1·17, SEM 0·284) in the patients while the mean (SD) value for the control group was 6·2 (2·01, SEM 0·539) (p<0·001) (Figure 2). The skin reactivity to dinitrochlorobenzene was grade 2 or less in 16 patients, while in the control group 13 had a response of grade 3 or 4. The mean (SD) value for the absolute B lymphocytes in nephrotics was 661 (391). In the control group it was 910 (512). The difference was not significant. The serum IgG concentrations in the nephrotic group was 576 mg% (SD 164, SEM 39) and in the controls was 1072 mg% (SD 348, SEM 93) (p<0·001).

The mean (SD, SEM) value for IgA concentrations in the patients with nephrotic syndrome was 87 (18, 4). In the controls it was 128 (32, 8). The difference was not significant. The IgM concentrations in the patients with nephrotic syndrome were 150 (SD 33, SEM 8). In the controls it was 140 (SD 41, SEM 11) (Figure 3). The serum complement concentrations in both the groups were within normal limits.

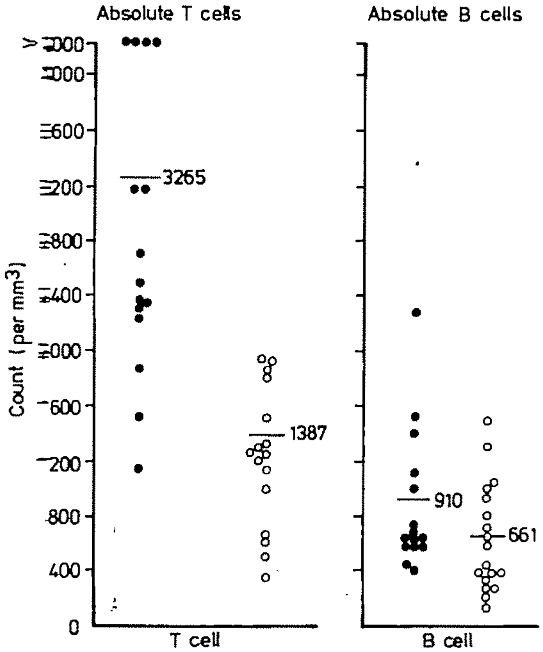

Fig. 1 *Absolute T and B cell lymphocyte counts in the group with minimal change nephrotic syndrome (n=18) and the control group (n=15).*

Patients with the syndrome are shown by o, controls by • (p<0·001 for absolute T cell count; p not significant for absolute B cell count). Values shown are the means.

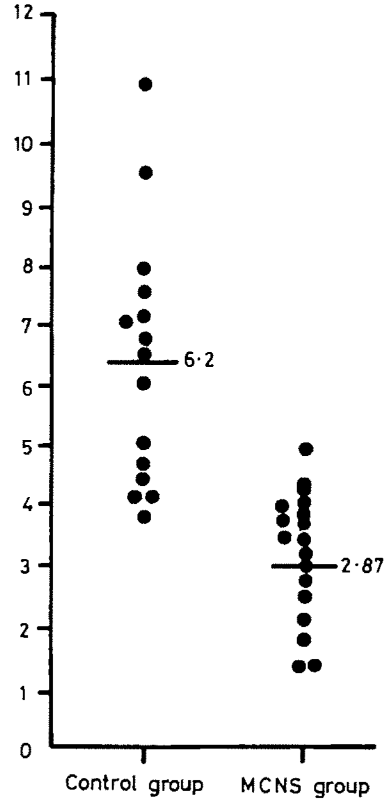

Fig. 2 *Blastogenesis index to phytohaemagglutinin stimulation at 72 hours in the group with minimal change nephrotic syndrome (MCNS) (n=18) and the control group (n=15).*

p<0·001. Value shown is the mean.

Results of treatment with levamisole. Fourteen patients with nephrotic syndrome were treated with levamisole. Their ages ranged from 1 to 12 years. Two were aged under 2, six between 2–5, and six over 5. There were eight boys and six girls. Six patients were seen in the first attack and had never received steroids, while out of the remaining eight cases responsive to steroids five infrequently relapsed and three frequently relapsed. One of those who frequently relapsed was also steroid dependent.

Of these 14 patients, six had complete remission, six had partial remission, and two did not respond to levamisole. The time taken to achieve remission varied from between four and 20 weeks of treat-

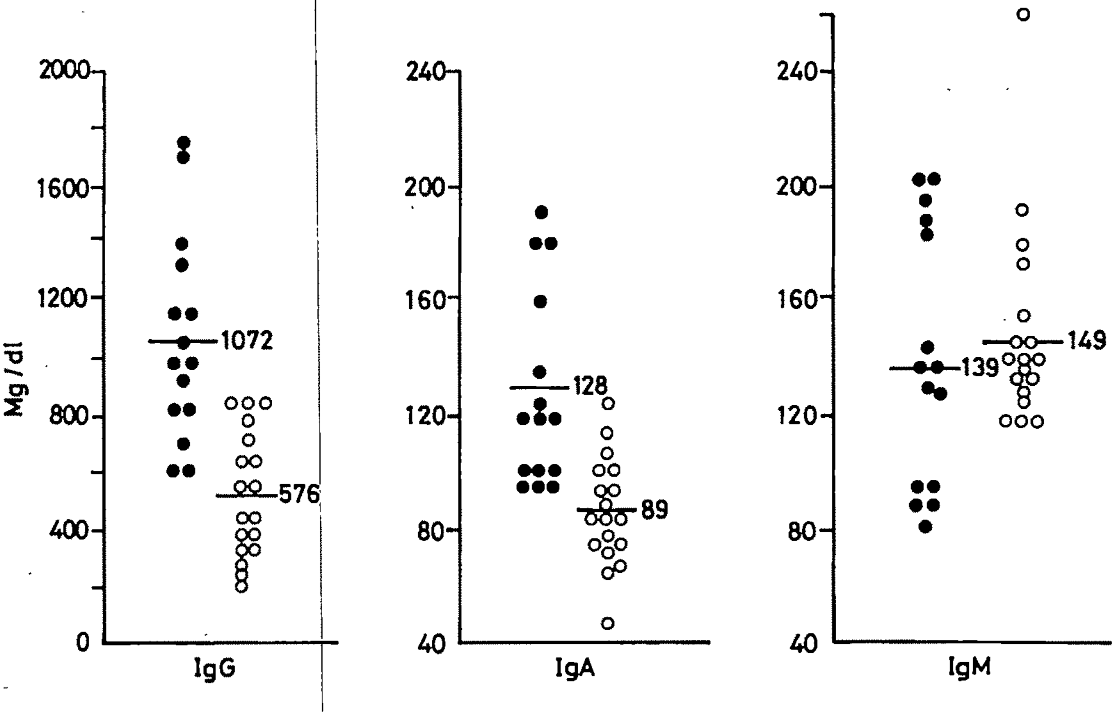

Fig. 3 *Serum IgA, IgG, and IgM concentrations in the group with minimal change nephrotic syndrome (n=18) and the control group (n=15).*

Patients with the syndrome are shown by o, controls by •. Values shown are the means.

ment, occurring slightly earlier (four to 12 weeks) in those who were on daily treatment. All the six patients aged over 5 showed a good response to treatment with levamisole; three went into complete remission and three into partial remission. Two patients who did not respond were aged under 5, one seen in first attack and the other who frequently relapsed. Of six patients seen in the first attack, four went into complete and one into partial remission. Of the five patients who infrequently relapsed, one went into complete remission and four into partial remission. Of these four in partial remission, two went immediately into complete remission after stopping treatment with levamisole. Of the three who frequently relapsed, one went into complete remission, one into partial remission, and one failed to respond. None of the 14 patients suffered from any severe infection during the six months. There was a reduced prevalence of infections most noticeable in six patients who had more than five episodes of severe infections in the previous year.

Side effects. Minor side effects were seen in those receiving daily treatment. These included vomiting in three cases, rash in one, and transient haematuria in two.

On follow up of 12 patients who showed an initial response to treatment with levamisole in the form of complete or partial remission, 6 months after stopping treatment, seven were in complete remission (five of six from the complete remission group, two of six from the partial remission group). Two were in partial remission, and three relapsed. Follow up of one to two years showed 7 of 12 in complete remission and 1 of 12 in partial remission.

Immunological studies after treatment with levamisole. T cell, B cell enumeration and blastogenesis index was repeated in two patients after remission induced by levamisole. In both these patients the blastogenesis index had increased. Immunoglobulins were repeated in seven patients. Six (five in complete and one in partial remission) showed increase in IgG concentration to more than twice the pretreatment values. In one patient in partial remission the IgG concentration was still low.

Discussion

Infections account for more than half the deaths due to minimal change nephrotic syndrome.[4] They are also responsible for the considerable morbidity seen in this disease. This increased vulnerability to infection can be accounted for by the depression in the immunological system as seen by the low cell count, depressed blastogenesis, poor skin reactivity to dinitrochlorobenzene, and low serum IgG concentrations.

Decreased response of lymphocytes to mitogens has been described in active nephrotic syndrome by several authors,[5–7] as has the poor skin reactivity to dinitrochlorobenzene.[5 8] Most authors, however, have reported the T cell to be numerically normal,[5 7] except in one other study by Tanphaichitr *et al* where the T cell counts were found to be low.[5] Low T cell counts were uniformly present in all our patients, only two of whom had received previous treatment with Endoxan, which is known to have a prolonged depressive effect on T cells.[10] Low serum IgG concentrations in relapse has been well documented and cannot be explained on urinary losses alone.[11 12]

It has not been established whether the depression in cell mediated immunity is a primary event or secondary to the hypoalbuminaemia, hyperlipidaemia, or zinc deficiency that coexists in these patients, as all these factors are known to depress cell mediated immunity.[13–15] It has been postulated that an abnormal immunogenic response to some unknown stimuli may be a primary event in patients with nephrotic syndrome, leading to suppression of T cell functions. This may lead to depressed cell mediated immunity as well as impairment of T cell dependent B cell activation accounting for the low concentrations of IgG in these patients. This same deviated immune response may be responsible for the production of an abnormal lymphokine with properties of increasing vascular permeability.[2] Such vascular permeability factors have been identified in the sera of patients with active nephrotic syndrome.[3]

Whether a cause or an effect, the immunological dysfunctions increase the risk of serious infections in these patients. The role of immunoregulatory drugs as opposed to immunosuppressive drugs in the management of these immunocompromised patients needs to be explored. Levamisole, used as an anthelminthic, has immunoregulatory properties. It is a non-specific stimulator of lymphocytes and has been found to increase both lymphocyte number and function. This action is particularly noticeable in immune depressed patients. It does not stimulate normal lymphocytes.[16] It has been successfully used in other immunologically mediated diseases such as rheumatoid arthritis, chronic active hepatitis, and recurrent skin infections.[16–18] Its successful use in minimal change nephrotic syndrome has been documented in a small number of children.[9]

We found that treatment with levamisole definitely reduced the number and severity of infections that in our experience often accompany or precede a relapse. This beneficial effect is probably due to its stimulant effect on cell mediated immunity. It has been used by some workers to treat certain varieties of recurrent and chronic infections with beneficial results.[16 17] Hence even in those nephrotics who have severe infections levamisole can be administered safely and probably to the advantage of the patient.

As opposed to this, steroids that act by depressing the T cell function increase the incidence and severity of infections, which may even be the cause of death in some instances.[4] In those patients presenting with infections treatment with steroids has to be postponed till the infection is well under control, thus delaying the beginning of definitive treatment. The effect of levamisole on the proteinuria, however, is slower and less dramatic compared with that of steroids.

In our study complete remission was achieved in six of 14 cases within 4–20 weeks of treatment. A total of 12 of 14 cases showed a definite reduction, however, in the proteinuria with improvement in the nephrotic state. Two of three patients who frequently relapsed benefited by this treatment. One went into complete remission, which was maintained for six months after stopping the drug; this child was steroid dependent, and this was the longest period free of disease that this child has had. The second patient who frequently relapsed remained free of both oedema and infection during the six months of treatment.

Several toxic effects, including agranulocytosis, have been described with the use of levamisole, especially in those receiving high daily doses.[16 19 20] In the schedule used by us there was no serious toxicity. Side effects are fairly common even with the recommended doses of steroids, while the dangerous side effects of prolonged treatment with steroids are well known.

Thus the role of levamisole in the management of minimal change nephrotic syndrome seems to be promising. The restoration of normal lymphocyte function by levamisole possibly helps to eliminate gradually the pathophysiological events leading to a nephrotic state. Further studies on the optimum dosage, regularity of administration, and duration of treatment require further investigation. Newer drugs with more specific actions on lymphocyte subpopulations may have a better role in the management of nephrotic syndrome.

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The sodium and potassium intake of 3 to 5 year olds

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SUMMARY The sodium intake of preschool children in their home environment was investigated and the major sources of sodium other than added table salt identified. Thirty five children from a Southampton general practice were studied. Twenty four hour urinary sodium excretion was measured as a reliable indicator of daily total sodium intake. The daily intake of sodium other than that from added table salt, and of potassium and other nutrients, was also calculated from three day dietary diaries collected using the household measures method. Median excretion of sodium was 62 mmol/24h (range 28–105, 28 urine collections) and of potassium was 25 mmol/24 h (range 14–46). The sodium:potassium ratio was 2·7 (1·4–5·2). From the diaries, the average daily intake of sodium was 68 mmol (32–98) and of potassium was 47 mmol (24–95), and the sodium:potassium ratio was 1·4 (0·5–2·7) (median and ranges, 35 children). Foods contributing more than 30 mmol sodium to one day's intake were mainly processed convenience foods.

The processes that lead to essential hypertension in adults are still not clear, but there is considerable evidence to support an interaction between genetic and environmental factors in determining blood pressure and occurrence of hypertension.[1,2] There are data to suggest some consistency of rank order of blood pressure during childhood from as early as 4 years of age,[3,4] and the idea has developed that essential hypertension is a process that starts early in life. If this is so, prevention may be possible through control of environmental factors in childhood.[1]

Excessive sodium consumption[5] or a diet low in potassium relative to sodium[6] have been incriminated as causative factors. Although neither has been proved definitely, recent nutritional guidelines for the United Kingdom recommend reduction in sodium intake that is thought to be needlessly high.[7,8] A World Health Organisation study group similarly recommended moderate reduction of the sodium intake of children.[1] A high sodium intake in early life may condition children to a lifelong high salt appetite.[9] In view of all the recent interest, it is surprising how little is known about the sodium consumption of young children in this country. Twelve Australian children aged 3–5 years had seemingly high sodium intakes, probably mainly from processed foods.[10]

This study aimed to evaluate the sodium intake of healthy 3–5 year olds living at home in Hampshire and to identify the major sources of dietary sodium other than added table salt.

Methods

Total sodium intake was assessed from 24 hour urinary sodium excretion. Dietary diaries obtained using the household measures method[11] were used to indicate the main food sources of sodium: quantities of foods eaten are described in terms of household measures such as cups or spoons. These are calibrated by the investigator and quantities converted to weights. To minimise the risk that salt consumption would change for the study, a preweighed salt shaker was not provided, and salt added during cooking was not quantified. An interest in dietary sodium was not mentioned to the mothers.

Fifty eight mothers with children aged 3–5 identified from the age and sex register of a Southampton general practice were invited to participate in a general study of children's diets. Mothers who agreed were visited at home during the period December 1984 to March 1985. They were asked to record details of all foods and drinks consumed by their child for three days, including one weekend day, and on one of the days to collect a 24 hour urine sample. At follow up visits details of the diaries were clarified, including the brands of foods, the volumes of utensils used were measured, and the children's heights and weights recorded. Food amounts recorded as volumes in the diaries were converted to the appropriate weights using tables of different foodstuff density. Foods were analysed for 28 nutrients using a computerised version of the McCance and Widdowson food composition tables[12] supplemented by values for British cooked dishes.[13] Totals for each day, and a three day mean, were calculated.

Urinary creatinine concentration was measured by a modified Jaffe reaction, using an LKB Reaction Rate Analyser (LKB Instruments Ltd, Surrey, England) and sodium and potassium concentrations with an ion selective electrode (Beckman Astra 8, Beckman Instruments Inc, California, USA). Urine samples collected for less than 21 hours were excluded, as were those with inappropriately low content of creatinine concentration. Electrolyte excretion of the remainder was adjusted to 24 hours. The Mann Whitney test and linear regression were used for statistical evaluation. The study had the approval of the local ethical committee.

Results

Thirty five children participated (a response rate of 60%) (Table 1). Two children achieved their sixth birthdays during the study. Most were within the expected range of weight for age and sex; five (14%) were below the 25th centile and 16 (46%) above the 75th centile, including five (14%) greater than the 97th centile. Quetelet's index (weight (kg)/height (m^2)) was used as an index of obesity.[14] When calculated using the rather unusual formula used in the DHSS survey in 1967–68:[15]

$$\frac{\text{Weight (kg)}}{\text{Height (cm}^2\text{)}} \times 1000$$

mean values of 1·66 and 1·69 were similar to that of 1·6 found for 3·5–4·5 year olds in the survey. The families were drawn from all social classes, with most from classes II and III.

Results from the urine collections (Table 2). Thirty one timed urine samples were obtained. Four children were uncooperative, ill, or incontinent. Three samples were rejected as being incomplete collections. The range of collection times of the remaining 28 samples was 21 to 25 hours, 24 being collected to within half an hour of 24 hours. The 24 hour sodium excretion for 15 boys (mean 67 mmol, range 52–95) and 13 girls (mean 63 mmol, range 28–105) did not differ significantly (Mann-Whitney test), and so the results for both sexes were combined. Sodium excretion was not correlated significantly with age, body weight, or obesity. The median values for sodium excretion of the small groups of children in each social class were similar.

Results from food table analysis of the dietary records. All the mothers completed the diaries, 31 for three days and four for two days. An average intake of each nutrient was calculated for each child (Table 3). The overall mean energy intake was 89% of the relevant recommended dietary allowances for age and sex.[16] The mean contributions of protein, fat, and carbohydrate to total energy intake were

Table 1 *Details of 35 children studied. Values are means (ranges)*

		Boys	*Girls*
No		19	16
Age (years)		4·5 (3·2–6·0)	4·6 (3·5–6·2)
Weight (kg)		19 (13·5–26·5)	20 (14·5–33·0)
Height (cm)		106 (95·5–115)	107 (98·5–123)
Surface area (m^2)		0·73 (0·58–0·90)	0·75 (0·62–1·03)
Quetelet's index (kg/m^2)		16·6 (13·8–20·1)	16·9 (14·8–21·8)
		All children	
Social class	I	2	
	II	8	
	III	16	
	IV	4	
	V	1	
	UE*	4	

*Father unemployed.

Table 2 *Results of urinary analysis of 28 samples corrected to 24 hours*

Excretion per 24 hours	*Mean*	*Median*	*Observed range*
Volume (ml)	581	543	273–1023
Sodium (mmol)	65	62	28–105
Sodium (mmol/kg body weight)	3·5	3·5	1·6–6·2
Sodium (mmol/m^2)	90	88	42–154
Potassium (mmol)	24	25	14–46
Sodium:potassium ratio	2·8	2·7	1·4–5·2
Creatinine (µmol/kg)	146	149	77–206

Table 3 *Results from food table analysis of the dietary records of the 35 children studied*

	Daily intake		
	Mean	*Median*	*Observed range*
Sodium (mmol)	69	68	32–98
Potassium (mmol)	50	47	24–95
Sodium: potassium ratio	1·5	1·4	0·5–2·7
Energy (kcal)	1455	1388	787–2204
Protein (g)	46	45	28–60
As % of kcal	12·7		9–17
Fat (g)	59	54	27–91
As % of kcal	36		26–46
Carbohydrate (g)	186	181	114–287
As % of kcal	51		38–60

similar to contributions of 11·5%, 38%, and 50·5%, respectively, found for children aged 3·5 to 4·5 years in the UK in 1967–68.[15] For the children as a group daily sodium intake calculated from the diaries was similar to that estimated more reliably from urinary sodium excretion (Tables 2 and 3). Although the two estimates were significantly correlated ($r=0{\cdot}4$, $p<0{\cdot}05$, $n=28$), the estimates differed in some individuals. This is to be expected considering the inherent inaccuracies of dietary diary analyses.

A highly significant negative correlation was observed between the ratio of sodium to energy intake (mmol/Kcal) and age ($r=-0{\cdot}63$, $p<0{\cdot}001$, $n=35$) and to body weight ($r=-0{\cdot}50$, $p<0{\cdot}01$, $n=35$). Age and weight correlated closely ($r=0{\cdot}69$, $p<0{\cdot}001$, $n=35$). This suggests that the young children had proportionately more sodium in their diet than the older children.

Potassium intake and sodium:potassium ratio. In this study the mean potassium intake estimated from the diaries of 50 mmol/24h (range 24–95) was higher than the mean urinary potassium excretion of 24 mmol/24h (range 14–46). This accounts for the lower sodium:potassium ratios calculated from the diaries (mean 1·5, range 0·5–2·7) when compared with urinary analyses (mean 2·8, range 1·4–5·2).

Foods contributing most sodium to the daily intake. The total number of days recorded in the diaries was 101. On 17 occasions a single foodstuff contributed more than 30 mmol of sodium in any one day (roughly half the mean daily intake for the group). This represented one helping, or several servings if the foodstuff was consumed more than once during the day, and accounted for 24–88% of the total sodium intake for that day (Table 4). Purchased processed foods were the main contributors, but cheese and a breakfast cereal were also included.

Table 4 *Foods contributing more than 30 mmol of sodium in any one day (101 days recorded)*

	mmol Of sodium per day	*% Of day's sodium intake*
Chicken soup, cream of, canned	85	88
Chicken noodle soup, dried	30	24
Faggots	64	49
Faggots	32	28
Faggots	32	33
Beefburgers, fried, frozen	54	53
Beefburgers, fried, frozen	30	44
Spaghetti, in tomato sauce, canned	43	42
Cheese, cheddar	42	37
Cheese, spread	36	36
Bacon gammon joint, boiled	40	37
'All Bran'	38	55
Meat pie	36	68
Baked beans, in tomato sauce, canned	35	51
Baked beans, in tomato sauce, canned	35	30
Baked beans, in tomato sauce, canned	34	47
Sausages, pork, fried	30	36

Discussion

The mean urinary sodium excretion of 28 children aged 3–5 in this study was 65 mmol/24h (range 28–105 mmol/24 h) and when related to body weight was 3·5 mmol/kg/24 h (range 1·6–6.2 mmol/kg/24 h). Non-renal losses of sodium in healthy children of this age are 3–4 mmol/24 h,[17] and apart from a small amount incorporated into growing tissues, any surplus sodium absorbed from the diet is excreted in the urine. Urinary sodium therefore reflects intake closely. The findings for our children were similar to those for 12 children aged 3–5 in Australia, whose urinary sodium on their normal diets was 28–121 mmol/24 h, with a mean of 67 mmol/24 h.[10] For comparison, most adults in the UK are estimated to have an intake of 7–12 g of sodium chloride, equivalent to 120–205 mmol of sodium.[7 8]

Are these intakes excessive? Maximum recommended sodium intakes for children are not well established. The estimated safe and adequate daily dietary intake recommended for 4–6 year olds by The National Academy of Sciences USA in 1980 was 20–59 mmol per day. The lower level was based on the average intake of breast fed 6 month old infants (26 mmol/m^2 per day) and the suggested upper level was three times this.[18] Safe tolerance limits for children were estimated rather arbitrarily by the US Academy of Pediatrics to be roughly 8–100 mmol/day, as the minimal requirements are around 8 mmol per day and infants can tolerate 100 mmol/day without adverse effects.[19] Thus in 17 (61%) of our 28 children sodium intake exceeded the US 1980 recommended allowances, but only one child had an intake above 'safe limits'. We do not have the facts to decide whether intakes of this order are harmful to children with a genetic risk of developing hypertension. An overall target intake for adults of 5 g sodium chloride per day (85 mmol of sodium) was proposed by WHO.[20] For a 70 kg adult with a surface area of 1·73 m^2 this is 1·2 mmol/kg per day, or 49 mmol/m^2 per day—rather less than the intakes of the children in this study.

Roughly 30% of the salt intake of adults in the UK is added at table or in cooking.[8] The close similarity of sodium intakes calculated from the dietary records in this study, which excluded added salt, to the estimates from the urinary sodium, which include sodium from all sources, suggests that added salt makes a relatively smaller contribution to total intake in young children. The major sodium sources without this were identified as mainly processed convenience foods such as beefburgers, baked beans, and soups—foods that the general public does not usually consider 'salty'. The children were not exposed to 'take away' foods, and their diets were not atypical in any obvious way. The mothers confirmed the long recognised problems of feeding younger preschool children, and many explained that their children refused the family meals and so were provided with separate 'acceptable' foods, which were generally some kind of processed foodstuffs. This might have accounted for the high sodium to energy intake in the younger children.

There is some evidence that a high potassium intake may protect against the hypertensive effects of sodium, and that exposure to a high sodium/low potassum intake may be a cause of hypertension in susceptible individuals.[7] There are no guidelines for the optimal dietary sodium:potassium ratio. In genetically salt sensitive rats a ratio of less than 2·0 protects against hypertension. The ratio in human milk is 0·6 to 0·7.[19] In adults the sodium:potassium ratio in urine has been used as an assessment of the dietary ratio.[6] The results from this study, however, suggest that this might be misleading in childhood, as the ratios calculated from the diaries were lower than those from the urinary analyses. The difference was attributable to the potassium content—median 47 mmol/24 hour from the diaries and 25 mmol/24 hour from the urine. Non-renal losses of potassium might account in part for the discrepancy, but there have been few carefully conducted electrolyte balance studies in healthy young children to provide firm data. On a dietary potassium intake of 2·27 (SD 0·80) mmol/kg per day the urinary potassium excretion of eight healthy children aged 6 months to 8·2 years was 1·36 (SD 0·51) mmol/kg/24 h (60% of the intake) and the faecal loss was 0·19 (SD 0·09) mmol/kg/24 h.[21] It is probable too, however, that short comings of the study also contributed to the difference. Collection of a single urine sample did not allow for day to day variations in potassium intake. Moreover, some of the data in the food tables is quite old and may not reflect accurately the potassium content of the modern preschool diet.

There seems little scope for mothers of young children to reduce the sodium intake much below that observed. Omission of table salt will help a little. Low sodium foods are generally expensive and not widely available. After 24 hours on a diet that contained no processed foods, the urinary sodium excretion of five Australian 3–5 year olds fell to 6–46 mmol/24 h (mean 19).[10] It seems that the only effective course would be to reduce the sodium added during manufacture of those foods which children like. Sodium salts are used for a variety of purposes in food processing. Sometimes there is not a safe or equally effective alternative, but the necessity for the use of sodium additives for flavouring might be questioned. There is clearly a need to establish definitely whether the amount of sodium consumed in childhood has any relevance to the later development of hypertension.[1]

We thank Dr T Rolles for allowing us access to her patients, Dr M Nelson for advice about dietary assessment, and Janet O'Clarey for help with the food table analysis.

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Fifty years ago

Reading difficulties in children

Mildred Creak (London)—Arch Dis Child 1936;**11**:143–156

Fifty children were studied who had been referred for difficulty in school work or were presumed to have such difficulties after interview. There were 38 boys and 12 girls between the ages of 6·3 years and 14·8 years. A variety of tests were given, including matching patterns, copying patterns, reproducing rhythms, and identifying wooden letters and numbers when blindfolded and also identifying them when traced on the back of the hand. Among the older children 'word tests' were used. 'The rhythm test separated out a small group of interesting cases. It was found that out of the fifty children, nine, who showed no difficulty in any other test, failed completely in this one. These were all children of good intelligence, with noticeable hyperkinesis, and with one exception outstandingly late in learning to talk. The association of a failure in auditory memory with retarded speech suggests an auditory factor.' When discussing 'Emotional Aspects' Dr Creak states 'By the time the case reaches the clinic the child has usually been accepted as 'silly' by fellow pupils and backward by his teachers. His grotesque compositions are held up to the class for ridicule. What is perhaps worse is when he is regarded as obstinate and constantly receives reports such as 'could do better if he tried and lacks concentration.''

(Dr Mildred Creak wrote this paper when she was physician in charge of the Children's Department, Maudsley Hospital, London. I had not read the paper before, which was my loss, as although the understanding of children's learning difficulties has undoubtedly improved among the various disciplines involved, so much of what Dr Creak says rings true today. Her 'subgroup' of children who failed on the 'rhythm test' is of particular interest in view of the recent work of Bradley and Bryant, who studied the hypothesis that children's experiences with rhyme and alliteration, which typically begin some time before they arrive at school, do have an influence on the progress they make in learning how to read and spell during their first years at school.[1] They found that their rhyming and alliteration scores bore a consistent and significant relation to progress in reading and spelling and that training these children to categorise words by their sounds improved their reading and spelling. This seemed to prove that the difficulties some children have in such learning can be attributed to a failure to master a phonological skill that comes naturally to most. NEIL GORDON.)

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Mild typhoid fever

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SUMMARY A series of 100 Zimbabwean children aged between 5 months and 13 years with culture positive typhoid fever is presented. The disease was found to be fairly mild with a low prevalence of complications, and no patient in the series died. Possible explanations for the relative mildness of typhoid in this paediatric population are discussed.

There are few reported studies of typhoid fever in children, and the available data suggests that its manifestations differ from those in adults.[1–4] There is also considerable geographical variation in the prevalence of complications and mortality in reported series.[1–3] An impression of a rather better outcome than is suggested by other reports prompted this review.

Patients and methods

The 100 cases were selected by retrospective review of admissions to the Harare Infectious Diseases Hospitals, and criteria for selection were that patients were: (a) below the age of 14 years; (b) symptomatic; and (c) culture positive for *Salmonella typhi.*

Patients were investigated in a standard manner. A single blood, three stool, and three urine specimens were cultured for *S typhi.* Stool and urine samples were also examined for ova and parasites. A full blood count, including platelet and reticulocyte counts, was performed on admission and repeated every seventh day during treatment. Other investigations were performed as dictated by the clinical findings and course. Antimicrobial treatment with chloramphenicol was routinely administered for 21 days by mouth unless vomiting precluded this, in which case it was given intravenously. Seventy two hours after completing treatment three stool and three urine specimens were cultured on consecutive days. If these were negative for *S typhi* the patient was discharged and was requested to attend for repeat cultures after one, three, six, and 12 months. Default from follow up was, however, the norm.

Results

Age, sex, and weight. The mean age of the 100 children was 7 years with a range of 5 months to 13 years. Figure 1 shows the distribution of patients throughout the age range, and while there was considerable variation between the different years there were no specific age peaks of incidence. There were 52 boys and 48 girls. The weight was recorded in 93 children, and in 53 (57%) it was below 80 per cent of the Boston 50th centile for weight. In six children (6%) the weight was below 60 per cent of the 50th centile.

Source of patients. Fifty nine of the patients came from rural areas within 250 km of Harare and 41 from the municipal area of Harare. In 23 patients one or more household contact was either a carrier or developed the disease.

Seasonal prevalence. Typhoid cases presented throughout the year but, as shown in Figure 2, which represents the 1984 admissions, there was a peak from December to February during the rainy season and a smaller peak in June.

Presentation. The mean duration of symptoms at presentation was 11 days (range 1–120). Fifty five

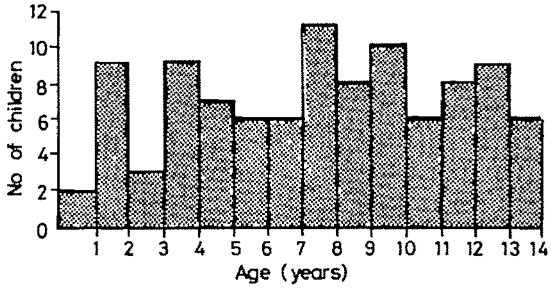

Fig. 1 *Age of presentation in 100 children with typhoid fever.*

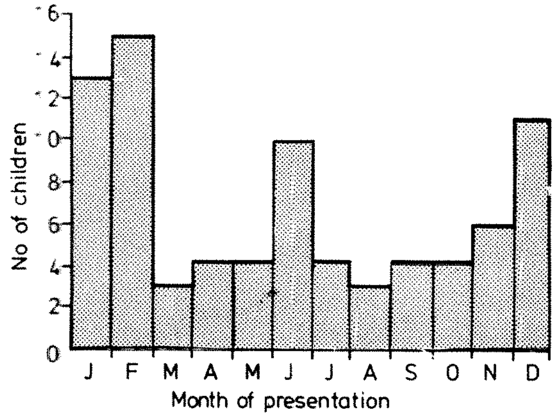

Fig. 2 *Seasonal prevalence of presentation in 100 children with typhoid fever.*

patients presented within seven to 14 days of the onset of symptoms. Table 1 shows the incidence of symptoms reported. Fever, headache, diarrhoea, and abdominal pain were the most common complaints. Three children were jaundiced on admission, and two of these had homozygous sickle cell disease. The other jaundiced child had raised transaminase activity, and *S typhi* was cultured from her blood.

One child presented with intestinal bleeding, and her haemoglobin concentration on admission was 42 g/l The bleeding settled within 24 hours of beginning treatment with blood transfusion and chloramphenicol. Another child with positive *S typhi* culture from the urine presented with features of the nephrotic syndrome, which resolved on treatment with chloramphenicol alone. A raised blood urea concentration of 22·6 mmol/l (136 mg/100 ml) was recorded in one child who was not clinically dehydrated, and this fell into the normal range after a few days of treatment.

One child presented with fever and extreme drowsiness, and another had slurred speech on admission, which resolved after seven days of treatment; another experienced auditory hallucinations for five days after admission and also had an abnormal electrocardiogram showing ventricular ectopic beats, which disappeared after a few days of treatment. A single case of meningitis was seen in a 5 month old baby who had a cerebrospinal fluid pleocytosis of more than 2000 white blood cells per centimetre but no growth on culture, though *S typhi* was isolated from the blood.

Clinical features. Table 2 shows the incidence of various clinical features. In common with other reports on paediatric typhoid fever there was no evidence of the temperature-pulse dissociation seen in adults.[2 4] Similarly, the leucopenia (white blood cell count less than $5\times10^9/l$) seen at the onset of adult typhoid fever was fairly uncommon and seen in only 26 patients. Splenomegaly was observed in 13, and a rash was seen in none. The typhoid state, characterised by blank facies and withdrawn demeanour, was seen in 17.

Laboratory investigations. The mean haemoglobin concentration on admission, excluding three children with homozygous sickle cell disease, was 99 g/l (range 36–141) and the mean total white cell count on admission was $7{\cdot}2\times10^9/l$ (range 2·1–31·1). Anaemia was common, and 32 of the 100 patients had an initial haemoglobin concentration of less than 90 g/l. The anaemia in most cases was normocytic and normochromic; the mean reticulocyte count on admission in 22 patients was 1·3%. Thirty six patients received a blood transfusion at some stage of the illness.

S typhi was cultured from the blood in 58 patients,

Table 1 *Presenting symptoms in 100 children with typhoid fever*

Symptom	*No of children presenting with symptom*
Fever	89
Headache	37
Diarrhoea	37
Abdominal pain	35
Vomiting	23
Cough	23
Limb pain	7
Weakness	4
Constipation	4
Jaundice	3
Gastrointestinal bleeding	1
Convulsions	1

Table 2 *Clinical features in 100 children with typhoid fever*

Feature	*No of children with feature*
Fever	95
Anaemia	32
Admission white blood cell count $<5\times10^9/l$	26
Hepatomegaly	22
Pulse rate <100 beat/min	17
Typhoid state	17
Splenomegaly	13
Chest signs	10
Abdominal tenderness	10
Dehydration	5
Confusion	3
Drowsiness	3

from the stool in 50, and from the urine in 12. Positive cultures were obtained from both blood and stool in 13 patients, from blood and urine in two, from stool and urine in three, and from all three cultures in one. Other pathogens were grown from the urine of four children; untyped coliforms in three and a salmonella species in one. Other stool pathogens were isolated on admission in four children; a Group C salmonella in two, a Group B salmonella in one, and in the fourth child both Group B and C salmonella. *Schistosoma haematobium* was detected in the urine of three children and *Schistosoma mansoni* in the stools of two.

Widal agglutination titres were measured in 43 patients. Eight had insignificant titres, while 35 had *S typhi* 'H' titre of 1/80 or an 'O' titre of 1/160 or higher. Sixteen had an 'H' titre and six had an 'O' titre of greater than 1/1280. Titres were measured on one occasion only in seven of the eight with insignificant titres and in 24 of the 35 with significant titres.

Chloramphenicol dosage. The mean dose of chloramphenicol per kilogram body weight per day was 64 mg (range 34–117). Most patients remained on the same dose throughout, but a proportion were reduced to 75% of the initial dose after one week of treatment.

Response to treatment. The mean period from onset of treatment to defervescence was five days (range one–12). Six patients failed to respond completely to treatment, in that 72 hours after stopping treatment they were still positive for *S typhi* –five in urine and one in stool. One of the six had a low grade fever, but the remaining five were asymptomatic and were therefore early carriers. Two late carriers were identified one month and two months after treatment, and symptomatic relapse occurred in two at one week and two months, respectively.

Mortality. None of the 100 patients in this series died. The zero mortality was conceivably due to the more seriously ill patients dying of typhoid fever at the two central hospitals before they could be transferred to the infectious diseases hospitals. A review was therefore undertaken of all typhoid admissions below the age of 14 to the central hospitals during the period of study, and only one death due to proved typhoid fever was encountered. This was due to intestinal perforation. Several other cases were recorded as typhoid deaths but no bacteriological, serological, or histological evidence confirmed the diagnosis.

Discussion

Typhoid fever is said to be milder in infants and young children,[5 6] and certainly the findings of this series suggest that this is so. It was previously thought to be rare below the age of 2 years,[7 8] but the Durban series[1] reported that 9% of their patients were under 2 years, which is close to the figure of 11% in this series. Other series have reported a similar pattern of presentation.[1–3] Gastrointestinal bleeding was seen in only one child, and other series report incidences between 0 and 13%.[1–3 9] Intestinal perforation was not seen in this series, and it has been suggested that perforation occurs less commonly in young children due to anatomical differences that result in more superficial ulceration of the Peyer's patches than occurs in older patients.[4] In this series 30 of the children were aged below 5, and in one Nigerian report no perforations were seen in 57 children below the age of 5 with typhoid fever.[10] In another Nigerian study no perforations were seen in children below 4 years.[9] A high incidence was reported from Ibadan, however, where 39% developed intestinal perforation.[3] A possible explanation is that only 17% of the 117 patients in that series were below the age of 5.

In conclusion, the severity of typhoid fever in children in this series was less than that described elsewhere,[1–3] and no deaths occurred. Case fatality rates in other recent series range widely from 0 to 32%.[1–3 9 10] There is no evidence to suggest that early referral was a factor in the generally favourable outcome as the mean duration of symptoms at presentation was similar to that reported in other series.[1–3] Nutritional state may be relevant in the outcome of this disease, but other studies have not specified the nutritional state of their patients to a degree that would make comparison possible. In spite of the fact, however, that 53 of these 100 children would be classified as undernourished by current definitions, response to treatment was in general satisfactory. The relative mildness of the disease in this study is possibly related to the intermediate state of sanitation currently prevailing in Zimbabwe. Exposure to *S typhi* early in life may provide a degree of immunity that reduces the severity of the disease occurring at a later stage.[5 8] Evidence for this was reported from this country by Wicks *et al*,[11] who found that over half of their 243 typhoid patients had *S typhi* 'O' or 'H' titres above 1/480 within seven days of the onset of symptoms, suggesting a primary immune stimulus in the past.

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Antinuclear antibody studies in juvenile chronic arthritis

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SUMMARY This study of children with chronic arthritis confirms that patients at greatest risk for chronic iridocyclitis have a young age of onset and positive antinuclear antibodies (ANA). Children who are ANA negative have a low risk of iridocyclitis. When it occurs it is at a significantly older age. No child developing juvenile chronic arthritis over 9, even with positive ANA, had chronic iritis.

There was remarkable variation in ANA titres; these correlated with erythrocyte sedimentation rate, active arthritis, and iridocyclitis. Maximum ANA titres were often seen very early in the disease but at this time were usually not associated with a poor prognosis.

Histocompatibility antigens A2 and DRw8 were significantly increased, suggesting primary associations in pauciarticular arthritis with ANA. HLA-DR5 was associated with mild forms of arthritis and with absence of, or only mild, iritis. HLA-B15/w62 was associated with severe forms of eye involvement.

Chronic inflammatory arthritis in childhood is known to encompass several subgroups with differing clinical and laboratory findings. Splitting patients into groups may help in the assessment of long term prognosis and management.[1]

Antinuclear antibodies (ANA) have been detected by immunofluorescence in roughly 30% of children with juvenile arthritis.[2 3] Patients who are ANA positive usually fall into one of three subgroups. The largest is children developing pauciarticular arthritis—that is, four or fewer joints affected—at a young age; they are predominantly girls and are prone to develop chronic iridocyclitis. ANA are also found among older children with a polyarthritis associated with IgM rheumatoid factor and less commonly among children with seronegative polyarthritis.

The occurrence of chronic iridocyclitis in seronegative juvenile chronic arthritis was first described by Ohm in 1910,[4] but it was not until 1974 that Schaller noted its close association with positive ANA. Possession of ANA, however, did not seem to predict whether a child's eye or joint disease would be mild or severe.[3] The terms chronic iridocyclitis, iritis, and uveitis are used interchangeably.

We have examined the longitudinal relation between ANA titres and disease activity in joints and eyes and have also looked at histocompatibility antigens (HLA).

Patients and methods

One hundred children with seronegative juvenile chronic arthritis referred to Taplow between 1970 and 1980 were identified as having had either positive ANA or chronic iridocyclitis, or both. The course of their joint and eye disease was charted using the number of active joints and the number of cells seen in the anterior chamber of the eye as indicators of activity. Erythrocyte sedimentation rate (ESR) and all ANA results were noted.

These patients underwent a clinical review between November 1981 and October 1982, and blood was taken for HLA antigens as well as ESR and ANA.

Disease pattern. Although most children with ANA and iritis have a pauciarticular onset of arthritis, it can extend to involve more than four joints. To define those children with a spreading arthritis the following terms were used, the onset time being the first three months.

(1) Persistent pauciarticular: never more than four joints involved.

(2) Pauciarticular in type: pauciarticular in onset and predominantly with four or fewer active joints, but up to a maximum of nine joints may be involved for periods of less than 12 months. This group includes children with more than four joints at onset who settle within a year to the pauciarticular pattern.

Children with pauciarticular pattern (both (1) and (2) above) were grouped as having mild arthritis.

(3) Extended pauciarticular: pauciarticular in onset but extending to involve more than four joints for periods of more than 12 months or to include more than nine joints in total.

(4) True polyarticular: more than four joints involved at onset and persistently thereafter.

Children with extended or polyarticular pattern ((3) and (4)) were classed as having severe arthritis.

Severity of chronic iridocyclitis. The overall severity was graded as follows:

(1) Mild: one to three bouts of iritis, settling rapidly with or without treatment.

(2) Moderate: chronic active iritis, usually requiring treatment but with periods of remission.

(3) Severe: secondary complications of cataract or glaucoma.

Laboratory data. ANA were measured by indirect immunofluorescence using rat liver substrate. Titres from our laboratory (in IU) and from other laboratories, where other results were used, were graded as shown in Table 1 using 1/40 as a cut off point.

Clinical and laboratory data were tested nonparametrically using Spearman's coefficient of rank correlation.

HLA typing was performed on all patients for HLA-A, B, C, and DR antigens using a panel of 240 established antisera and taking particular care with the cross reacting specificities DR5, DRw6, and DRw8. Controls for the HLA data were 192 random, normal unrelated subjects. For HLA statistical analysis six children were excluded, four on grounds of nationality and two because an affected sibling had been included.

Antigen frequencies between different groups of patients were compared using 2×2 contingency tables, and the significance of associations was assessed by means of χ^2 calculations (with Yates's correction) and/or calculation of Fisher's exact probabilities. Few of the apparent antigen correlations with subgroups of patients remained significant when probabilities were corrected to allow for the number of comparisons performed, though their significance may be confirmed when viewed in the light of other studies. Probabilities quoted are therefore uncorrected.

Table 1 *Titres of antinuclear antibodies graded using 1/40 as a cut off point*

	Grade			
	Negative	*Positive*		
	0	*1*	*2*	*3*
Titres	1/10	1/40–1/80	1/160–1/640	≥1/1280
Taplow 1974→	6	25	100–400	≥1600
Taplow 1970–73	1	31	158	≥315

Results

Duration of disease and sex. The mean duration of disease was 9·5 years with a range from 4·4 to 38 years. There were 75 girls and 25 boys, with no significant differences between the subgroups in the frequency of occurrence of ANA, nor severity of arthritis or iritis.

Disease pattern groups. There were 67 children with both ANA and iritis, 27 with ANA alone, and six with iritis alone (Table 2). Ninety patients had a pauciarticular onset of arthritis, and 25 remained persistently pauciarticular. Thirty four patients were classed as pauciarticular in type, and this included four patients with more than four joints involved at onset. Thirty five children had extended pauciarticular disease. Six were classed as true polyarticular, including one boy with systemic features.

Table 2 shows the distribution of ANA and iritis

Table 2 *Distribution of antinuclear antibodies and iritis by disease pattern for 100 children with juvenile chronic arthritis*

	Mild		*Severe*		
	Persistent pauciarticular	*Pauciarticular in type*	*Extended pauciarticular*	*True polyarticular*	*Total*
Antinuclear antibodies and iritis	14	25	23	5	67
Antinuclear antibodies alone	10	9	8	0	27
Iritis alone	1	0	4	1	6
	25	34	35	6	100

by disease pattern; there were no significant differences in the subgroups. Table 3 shows the even distribution of severity of eye involvement according to possession of ANA.

Age of onset. The mean age of onset of disease was 3·7 years with a range from 6 months to 15 years (Figure 1). Altogether, 79 had an onset under the age of 5 and 95 under the age of 10. Only five (38%) of the 13 children who developed arthritis aged 6 or more subsequently developed iritis compared with 22 (81%) of the 27 with onset under 2.

The mean age of onset was significantly less in the group with both ANA and iritis (3·0 years) than in those with ANA alone (5·1 years) (p=0·002). All five patients with onset aged 10 or more were in the group positive for ANA but without eye disease. The children with iritis alone had an intermediate age of onset of 4·1 years.

The mean age of onset of uveitis was 5·8 years, but there was a significantly older age of onset in the ANA negative patients (14·0 years) compared with the ANA positive patients (5·1 years) (p<0·001).

The mean time between onset of arthritis and discovery of iridocyclitis was 2·7 years (Figure 2). Three patients developed iritis before arthritis with a mean time difference of nine months.

When the severity of eye disease was assessed the age of onset of arthritis was not an indication of the severity of outcome, but there was a trend towards those with a late onset of iritis having relatively mild involvement, especially in the few patients where it developed more than five years after the arthritis.

Table 3 *Distribution of severity of eye involvement according to possession of antinuclear antibodies in 100 children with juvenile chronic arthritis*

Antinuclear antibodies	*Severity of eye involvement*				*Total*
	None	*Mild*	*Moderate*	*Severe*	
Positive	27	18	16	33	94
Negative	—	2	0	4	6
	27	20	16	37	100

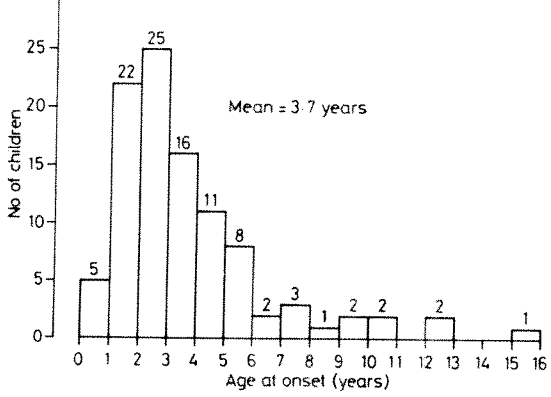

Fig. 1 *Age of 100 children at onset of juvenile chronic arthritis.*

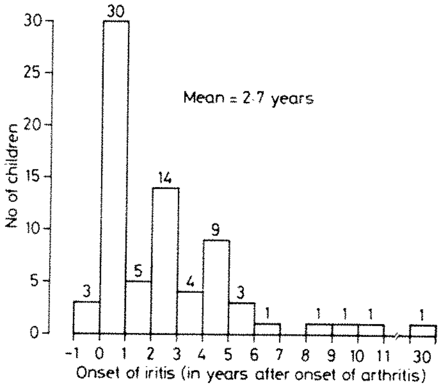

Fig. 2 *Time between onset of arthritis and onset of iritis in 73 children.*

Data evaluation. Data on the patients included 590 active joint and eye assessments and 415 ESR and 388 ANA estimations. There was a highly significant association of active joint count with high ESR ($p=0\cdot01\times10^{-4}$). ANA titres also correlated with ESR (p=0·005), with active joints ($p=0\cdot03\times10^{-5}$), and with active iritis (p=0·01).

At the two, five, and 10 year follow ups there were significant associations of both active joint count and ESR with overall severity of arthritis (all p=0·002), except for the ESR at two years. After 10 years of disease children with extended pauciarticular and true polyarticular arthritis still had 4·6 and 10·3 active joints, respectively.

Of the patients who had ANA titres estimated at these three follow ups, there were no significant associations of mean ANA with severity of disease, though the persistent pauciarticular group almost always had lower mean titres than other groups (range 0·5 at 10 years to 0·9 at 2 years). The extended pauciarticular group maintained their positive ANA (mean 1·2) up to 10 years and this paralleled their persistent mean active joint count of 4·9 and ESR of 37·5.

At five years ANA titres correlated with active joint counts (p=0·03), activity of iritis (p=0·025), and ESR (p=0·006). These associations did not reach significance at either two or 10 years when there were fewer results available for analysis.

Variation in ANA titres. There was considerable variability in the readings recorded in the individual patients. Six children were persistently ANA negative and 43 persistently ANA positive, although only seven had the same titre at each recording. Fifty one had at least one negative ANA during the course of their disease, including 17 who were negative when first tested. Thirty two children who had become ANA negative at the last follow up showed a trend towards milder eye and joint involvement, which had often become inactive.

First ANA recorded. The first ANA titre in each patient who then or subsequently became ANA positive was graded as described in Table 1. The mean titre was highest (2·10) in children tested within three months of onset falling to 1·87 in the first year of disease and 1·43 overall.

Maximum ANA recorded. The maximum ANA recorded in each patient was charted and most (54%) had a grade 2 positive ANA, with 18% having grade 1 only and 22% having a maximum grade 3. The proportion of patients with strongly positive ANAs (grade 3) was significantly greater in the two groups with severe arthritis than in those with milder disease, while the proportion did not vary significantly between groups according to severity of uveitis.

Among the 22 patients with grade 3 positive ANAs the mean time from date of onset of disease to maximum ANA was only 1·5 years in those with mild arthritis compared with 5·0 years in the severely affected group ($p=0{\cdot}04$).

ANA before or at onset of chronic iridocyclitis. Of the 67 patients with ANA and iritis, only 13 had had ANA tested more than three months before its onset. Eight of 11 who had been previously positive remained so and two who had been initially ANA negative became positive at the time of onset. Of a further 25 patients who had ANA tested at or within three months of onset of iritis, 20 were positive, and three of the other five became positive when the test was repeated within six months.

Chronic iridocyclitis with negative ANA. Of these six patients (Table 3), three were girls and three boys. All had had at least three negative readings, including ANA at the time of onset of iritis in four and during periods of activity in four. Three patients had some atypical features of disease with one having bouts of acute as well as chronic iridocyclitis.

Table 4 *Prevalence of HLA antigens in 94 children with juvenile chronic arthritis and 192 control patients*

Antigen	*Patient %*	*Control %*	*p Value**
A2	76·6	46·8	$0{\cdot}1\times10^{-5}$
B15/w62	21·3	9·3	0·004
DR5	30·9	14·1	$0{\cdot}09\times10^{-2}$
DRw6	38·3	22·4	0·004
DRw8	39·4	2·7	$0{\cdot}1\times10^{-12}$

*Fisher's exact test.

HLA antigens. There were significant increases in HLA antigens A2, B15/w62, DR5, DRw6, and DRw8 in our children compared with controls (Table 4). A2 and DRw8 were found throughout the group with no variation according to severity of arthritis. The increases in B15/w62, DR5, and DRw6 were only in the two groups with mild arthritis with no significant increase in the severely affected children when compared with controls.

The frequency of the A2 antigen was roughly the same in all grades of severity of uveitis. The frequency of DR5 was significantly higher in that group of patients with no or only mild eye disease than among controls ($p=0{\cdot}03\times10^{-3}$).

The frequency of DRw8 was increased above controls in all categories of eye involvement. The frequency, however, was significantly higher among patients with mild or no iritis than among patients with moderate or severe eye disease ($p=0{\cdot}01$).

In children with iritis there was an increase in B15/w62 compared with those without iritis. In those with moderate and severe iritis this was significant even after correction for the number of B antigens tested ($p=6{\cdot}9\times10^{-4}$).

Discussion

In young children with pauciarticular onset juvenile arthritis the association of ANA with chronic iritis and the HLA anitgens DR5 and DRw8 has been well documented.[2 3 5-10] In previous studies ANA have been shown in between 4%[11] and 88%[3] of patients. ANA has only been measured, however, at one point, sometimes very early in the disease[2] and sometimes late, when most children had inactive arthritis.[11] There were varying groups of children in each paper, including seropositive arthritis in five,[2 7 12-14] and only two groups particularly studied those with iritis.[3 15] This study has selected patients with a very high incidence of positive ANA (94%).

We confirm the very young age of onset of 3·0 years in those with both ANA and uveitis; this was significantly younger than those children with positive ANA who did not develop eye disease. The mean time between onset of arthritis and discovery of iritis was 2·7 years, but 45% of children developed it within 12 months of the onset of their arthritis. We suggest, therefore, that during this early period patients at risk should have slit lamp examinations at least every three months to detect iridocyclitis.

Previous studies have usually measured ANA at only one point. Hanson noted considerable variability in ANA positivity and titres over time but did not mention any associations.[16]

In those studies that looked for a correlation between disease activity and ANA titres, three found no relation with active arthritis,[3 6 7] and only one correlated complement fixing granulocyte specific ANA in undiluted serum with both disease activity and high ESR.[5] Similarly, three reports showed no relation between ANA titres and activity of iritis.[3 5 15] One group found that eye involvement, rather than current activity, correlated with complement fixing ANAs in the small number of patients studied.[15]

In this longitudinal study we have been able to show a greater variation in ANA titres and would suggest that by taking serial estimations of ANA at different stages in the course of the disease a more sensitive relation with active joints, ESR, and active iritis has emerged. A high ANA titre in the early stages of disease was not uncommon and tended to be associated with milder forms of arthritis, particularly if later ANA titres had fallen to grade 1 positive or negative. Persistent moderately positive ANAs or those rising to maximum titres after several years of disease were often associated with more severe arthritis.

A positive ANA in any child with seronegative chronic arthritis is a marker for the possible development of uveitis, whether the ANA is present initially or develops several months or years into the disease. As many children carry ANA in the absence of uveitis, this is obviously not a specific stimulus to ANA formation, and we do not know the nature of the nuclear antigens involved. There certainly seems to be a difference between the ANA in juvenile chronic arthritis and that in patients with systemic lupus erythematosus,[14] and further immunological studies may help to characterise the antigens involved.

Our HLA studies found a very high frequency of HLA-A2, suggesting a primary association with all types of pauciarticular onset arthritis, whether associated with ANA or iritis, or both. The positive associations with the DR antigens 5, w6, and w8 are also striking, and the increase in DRw8 to a frequency 15 times higher than in the controls suggests the presence of a linked disease gene conferring susceptibility to pauciarticular onset arthritis associated with ANA. By contrast, DR5 and DRw6 are only increased in the mild forms and not in the more severe arthritis.

The antigens DR5 and DRw8, present in the highest frequencies, showed a significant trend to associations with the absence of, or only mild, iritis despite being linked to positive ANA. The finding of B15/w62 being associated also with mild arthritis but with the more severe forms of eye disease is interesting and will require confirmation from other groups.

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Abnormalities of vascular prostaglandins in Henoch-Schönlein purpura

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SUMMARY The ability of plasma to support prostacyclin like activity from human umbilical arterial rings was studied in 17 patients with Henoch-Schönlein purpura and 17 controls matched for age and sex. Plasma from 13 of the 17 patients showed a diminished or absent ability to support prostacyclin like activity in vitro. Six patients whose plasma had a low or absent ability to support prostacyclin like activity showed evidence of inhibitory activity. Plasma from three of these patients also failed to preserve the effect of a stable prostacyclin like analogue (ZK36–374). The plasma concentration of prostacyclin metabolite and the serum concentration of thromboxane A_2 metabolite, thromboxane B_2, were measured simultaneously. The concentration of plasma prostacyclin metabolite in 10 of the 14 patients was decreased, and a positive correlation was found between the plasma prostacyclin metabolite values and the ability of the plasma to support prostacyclin like activity. There was no significant difference in the serum thromboxane A_2 metabolite concentrations between the patients and controls. These data suggest that abnormalities of vascular prostaglandin metabolism are involved in the pathophysiology of Henoch-Schönlein purpura.

Key for abbreviations used in text

PGI_2: prostacyclin.

PSA: estimation of ability of plasma to support vascular PGI_2 like activity.

PSAI: inhibition of vascular PGI_2 like activity.

PGI_2m: prostacyclin metabolite.

TxB_2: thromboxane A_2 metabolite.

Henoch-Schönlein purpura is the most commonly encountered type of vasculitis in childhood. The skin lesions are the most obvious sign, but visceral involvement carries a more serious prognosis. In two thirds of patients arthritis and gastrointestinal involvement occur, and in a minority of patients, in addition, the central nervous system is involved. Renal involvement, however, is potentially the most serious manifestation as chronic renal impairment may develop.[1 2] The aetiology and pathogenesis are obscure, but the primary manifestations are due to inflammation of small non-muscular vessels.[3] Henoch-Schönlein purpura may follow exposure to drugs or allergens[4] and is in many cases preceded by upper respiratory tract infection occasionally caused by group A β-haemolytic streptococci.[3] None of these factors, however, have been confirmed to be of pathogenetic importance.

Increased number of data are now available about the possible role of vascular prostaglandins prostacyclin (PGI_2), and thromboxane (TxA_2) in the pathogenesis of other vasculopathies. PGI_2 is an unstable substance with potent antiaggregatory and vasodilatory activity,[5] synthesised from arachidonic acid by the vessel well cycloxygenase system.[6] TxA_2 is also an unstable endoperoxide with vasoconstricting and platelet aggregatory activity,[7] derived from arachidonic acid predominantly by the platelet cycloxygenase system.[8] Remuzzi *et al* first showed deficient PGI_2 production in the haemolytic uraemic syndrome and the related disorder of thrombotic thrombocytopenic purpura. Plasma taken from these patients had a low capacity to support PGI_2 production in vitro from rat aortic rings.[9] Reduced umbilical and placental vascular PGI_2 has been observed in patients with severe pre-eclampsia.[10] Saldeen *et al* have reported an increased concentration of TxA_2 and PGI_2 metabolites in patients with deep venous thrombosis,[11] and increased TxA_2 synthesis by platelets has been shown in Kawasaki disease.[12] We report our preliminary findings on various aspects of vascular prostaglandin metabolism in the acute phase of Henoch-Schönlein purpura.

Patients

Seventeen patients with Henoch-Schönlein purpura aged between 2 and 13 years (mean (SD) 5·7 (2·5) years) and 17 controls matched for age and sex were studied. The control children were free of renal, cardiovascular, pulmonary, and inflammatory disease and were admitted for minor surgical operations. All patients had the classical purpuric rash, and in 13 cases the skin lesions were associated with joint manifestations. One child had recurrent purpura, and none of the patients had hypertension. In eight cases gastrointestinal symptoms were observed, and this included one patient who required operative intervention for ileocolic intussusception. Three patients had a mild illness without abnormal urinalysis or abdominal or joint manifestations. In eight patients haematuria (>10 red blood cells/μl) and/or proteinuria (31 (SD 19) mg/hr/m^2), was observed. There was no significant difference in the creatinine clearance between those patients with abnormal urinalysis (94 (SD 33) ml/min/1·73 m^2) and those with normal urinalysis (100 (SD 21) ml/min/1·73 m^2). In all patients plasma albumin concentrations, plasma electrolyte concentrations, and blood film showed no abnormalities, and the mean platelet count was 357 (SD 54)×10^9/l.

Methods

After informed consent had been obtained 10 ml of venous blood was taken from the controls and from the patients during the acute phase of the disease, 1–5 days after the occurrence of the rash. Blood for estimation of the ability of the plasma to support PGI$_2$ like activity (PSA) was anticoagulated with 3·2% trisodium citrate in a ratio of 9:1. Samples for PGI$_2$ metabolite (PGI$_2$m) measurements were collected into ice cold plastic tubes anticoagulated with 1:9 volume 3·8% w/v trisodium citrate: 3×10^{-5}M indomethacin: 10^{-4}M adenosine. Tubes were kept on ice and spun within one hour at 4°C and 2500 *g*. Plasma was separated and stored at −70°C. Samples of this pool were included in each assay both at the beginning and end to determine reproducibility and to act as a standard. A known amount of 6-keto PGF$_1$α was added to an aliquot of this pooled plasma to estimate recovery.

Platelet poor plasma, obtained for PSA estimation, was prepared within 20 minutes of collection by centrifugation at 2000 *g* for 10 minutes at 4°C. Simultaneously, serum samples were separated for estimation of TxB$_2$ (stable metabolite of TxA$_2$). All plasma and serum samples were stored at −70°C until examination.

Platelet rich plasma for aggregation studies was prepared from normal adults by centrifugation of citrated plasma at 800 *g* for 10 minutes at room temperature. The final platelet count was adjusted to 250–300×10^9/l by dilution with autologous platelet poor plasma. No patient or control was taking any drug known to alter prostaglandin metabolism for at least two weeks before the study.

Estimation of ability of plasma to support vascular PGI$_2$ like activity (PSA). The ability of test plasma (patient and control) to support PGI$_2$ like activity was assessed by measurement of platelet antiaggregatory activity by the method of Moncada *et al.*[13] Human umbilical arterial rings were obtained from freshly delivered umbilical cords. The umbilical arteries were freed from all surrounding tissue, cut into rings 1 mm in length (30–50 mg wet weight) and kept in Ringer's buffer (pH 7·4) at 0°C for not more than 60 minutes. The rings were then incubated in 1 ml tromethamine buffer (pH 8·6) for five minutes at 37°C, and PGI$_2$ like activity (platelet antiaggregatory activity) of 100 μl of the supernatant was tested. This was added to 200 μl platelet rich plasma in a Servogor 120 dual channel aggregometer. The mixture was incubated for one minute at 37°C, then collagen (Hormonochemie), at a final concentration of 2 μg/ml, was added. The rate of aggregation was recorded using a Malin platelet aggregation recorder.[14] The rings were then washed several times with Ringer's buffer at 37°C until no antiaggregatory activity could be detected. These exhausted rings were then incubated with 1 ml of test platelet poor plasma at 37°C for 20 minutes. PGI$_2$ like activity was then assessed as before. The ability of each test platelet poor plasma to support PGI$_2$ like activity was expressed by calculation of the percentage difference in inhibition of platelet aggregation obtained by the same exhausted ring before and after the addition of test platelet poor plasma.

Detection of inhibition against PGI$_2$ like activity (PSAI). To detect inhibitory activity in the test plasma a modified method of Levin *et al* was used.[15] Fresh, unexhausted umbilical arterial rings were incubated in phosphate buffered saline (pH 7·4) at 37°C for five minutes. The PGI$_2$ like activity of the supernatant was compared with that produced by the same ring after five minutes incubation with test platelet poor plasma.

Preservation of PGI$_2$ like effect of stable PGI$_2$ analogue. The preservation of PGI$_2$ like effect of a stable PGI$_2$ analogue, ZK36-374 (Schering chemicals AG), was assessed using test platelet poor plasma. ZK36-374, at a final concentration of 100 ng/l, was incubated with 300 μl of test platelet poor plasma at 37°C for five minutes. The concentration of ZK36-374 corresponded to that concentration known to have a definite antiplatelet effect when the drug is given by intravenous infusion.[16] Then 100 μl of the supernatant was removed and added to 200 μl platelet rich plasma. After one minute of incubation and stirring, platelet aggregation studies using collagen were carried out as before. After incubation of normal plasma with ZK36-374 total inhibition of platelet aggregation should be expected due to the protective effect of the PGI_2 analogue.[16]

Radioimmunoassay studies of plasma PGI_2m and serum TxB_2. Plasma concentrations of PGI_2m were assessed by radioimmunoassay using a modification of the method of Mitchell.[17] As only 40% of PGI_2 is metabolised to 6-keto $PGF_1\alpha$ we used an assay that measures in addition the more labile metabolites.[18] The measurement was carried out on unextracted plasma buffered with 0·1% bovine albumin, as many extraction techniques may add further impurities.[19] Our method gives good reproducibility and recovery of added PGI_2m and has a sensitivity of 5 pg/ml.[20] Serum TxB_2 was measured using a radioimmunoassay method as described by Granstrom and Kindahl.[21]

All platelet aggregation and radioimmunoassay studies were carried out in duplicate. Statistical analysis was carried out using the Student's *t* test and Spearman rank correlation test.

Results

Ability of plasma to support PGI_2 like activity was reduced in 13 of the 17 patients with Henoch-Schönlein purpura studied. In five cases PSA was undetectable (Fig. 1). The difference between the results of the patient group (21·3 (SD 20·5)%) and the control group (57·2 (SD 12·2)%) was significant ($p<0·001$). In addition, the results of those patients with abnormal urinalysis and gastrointestinal involvement (7·5 (SD 18·1)%) was significantly different from the results of those patients with neither of these manifestations, (32·3 (SD 23·5)%) ($p<0·01$).

Detection of inhibition against PGI_2 like activity (PSAI). Plasma from six patients in which the PSA was low or absent was further investigated to detect PSAI. Less PGI_2 like activity was produced by the unexhausted umbilical arterial rings when incubated with platelet poor plasma from the six patients than with either phosphate buffered saline or control platelet poor plasma (Table).

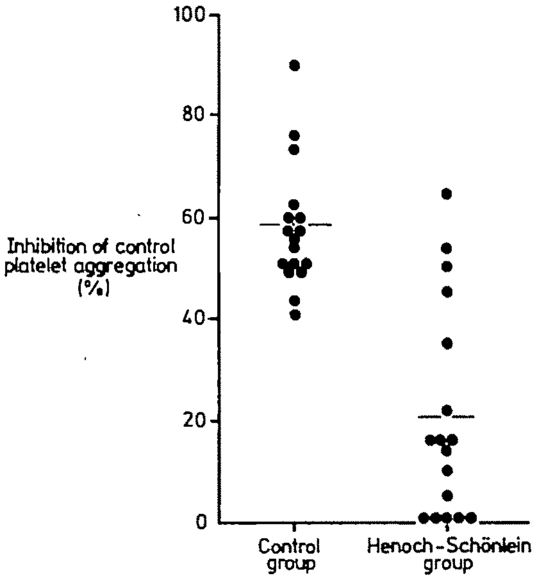

Fig. 1 *Ability of plasma to support vascular PGI_2 like activity (PSA) in patients with Henoch-Schönlein purpura.*

Table *Plasma factors influencing prostacyclin (PGI_2) like activity in Henoch-Schönlein purpura*

Case No	*PSA* (%)*	*PSAI†*	*Preservation of ZK 36-374‡ effect*
		Patients	
1	0	+	Normal
2	0	+	Decreased
3	0	+	Decreased
4	0	+	Decreased
5	0	+	Normal
6	23	+	Normal
		Controls	
1	62	−	Normal
2	57	−	Normal
3	65	−	Normal

*Estimation of ability of plasma to support vascular PGI_2 like activity.
†Inhibition of vascular PGI_2 like activity: + = present, − = absent.
‡A stable PGI_2 like analogue.

Preservation of PGI_2 like effect of stable PGI_2 analogue. The effect of ZK36–374 was noticeably depressed after incubation with platelet poor plasma from three of the six patients in whose plasma PSAI was present (Table).

Plasma PGI_2m and serum TxB_2. There was a significant difference between the results of plasma PGI_2m concentrations obtained from 14 patients with Henoch-Schönlein purpura (16·6 (SD 8·7) pg/ml) and the control group (35·3 (SD 7·5) pg/ml)

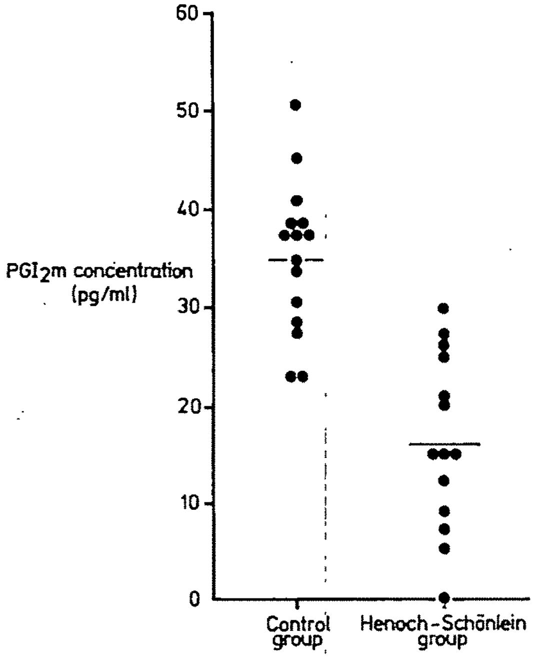

Fig. 2 *Plasma PGI_2 metabolite (PGI_2m) concentrations in patients with Henoch-Schönlein purpura.*

($p<0{\cdot}05$) (Fig. 2). A positive correlation was found between PSA and PGI_2m values ($r=0{\cdot}52$, $p<0{\cdot}05$). There was no significant difference in serum TxB_2 concentration between the 16 patients (11·4 (SD 9·4) ng/ml) and the control group (13·2 (SD 8·6) ng/ml). No significant correlation was found between the results of the tests on serum TxB_2 and plasma PGI_2m concentrations.

Discussion

It is well known that the pathological defect in Henoch-Schönlein purpura is that of a predominantly small vessel vasculitis. Abnormalities of vascular prostaglandin metabolism have been documented in other vasculopathies, particularly in the haemolytic uraemic syndrome. There are, however, no published reports of studies in Henoch-Schönlein purpura. Conceivably, after an endothelial insult, such as deposition of immune complexes, a defect of PGI_2 generation may be present.

We have shown that plasma from patients with Henoch-Schönlein purpura in the acute phase of the illness has a diminished or absent ability to support PGI_2 generation in vitro from human umbilical arterial rings. Absent or depressed PSA concentrations may theoretically be due to a number of causes, occurring singly or in combination. Firstly, a decreased ability of the plasma to stimulate PGI_2 production;[9] secondly, the presence of inhibitory activity in the plasma either to the production[15] or to the effect of PGI_2;[22] and thirdly, rapid degradation of stimulated PGI_2.[23] All six patients in this study who had very low or absent concentrations of PSA, in whom further investigation was carried out, showed the presence of PSAI. The presence of PSAI may mean inhibitory activity against PGI_2 production, inhibitory activity against PGI_2 effect, or increased PGI_2 degradation. To attempt to differentiate these possibilities we looked at the ability of test plasma to preserve the effect of a stable PGI_2 analogue (ZK36-374) and found this to be absent in three of the six patients studied. The concentration of ZK36-374, although significantly higher than the physiological concentrations of PGI_2m in both patients and controls, was chosen because a definite antiplatelet effect was desired. It would be interesting to undertake further studies using different concentrations of the PGI_2 analogue; however, this was outwith the scope of this present study. On the basis of these data it would seem that in patients with low or absent concentrations of PSA inhibitory activity may exist to either PGI_2 production or PGI_2 effect.

We have also shown that most patients with Henoch-Schönlein purpura in this study had a decreased concentration of plasma PGI_2 metabolite (PGI_2m). It is of interest, however, that two patients showed a fairly high concentration of PGI_2m in combination with a low or absent PSA concentration and plasma inhibitory activity to the effect of the stable PGI_2 analogue. This would tend to confirm the presence of a circulating inhibitor to PGI_2 effect in these cases. These findings also show that platelet aggregation studies are more sensitive in detecting decreased PGI_2 like activity of plasma than determination of PGI_2m concentration.

We have found no significant difference in serum thromboxane (TxB_2) concentrations between the patient group and the control population. Furthermore, there was a poor correlation between the concentration of serum TxB_2 and plasma PGI_2m concentrations. These results do not suggest the presence of platelet activation in this syndrome. In view of the small numbers of patients in this study and the absence of any follow up data we felt unable to attempt a correlation between the demonstrated abnormalities and the clinical picture. It is of interest, however, that patients whose clinical picture included abnormal urinalysis and gastrointestinal involvement had a mean PSA concentration that was significantly depressed compared with those patients in whom these clinical manifestations were absent.

The above findings suggest the abnormality of PGI_2 metabolism in Henoch-Schönlein purpura is rather complex and heterogenous. Further studies will be required to define the biochemical nature of the inhibitors and to establish whether low or absent PSA concentrations always reflect the presence of inhibitory activity and whether there is any evidence of rapid PGI_2 degradation. It seems likely that these abnormalities, having been shown in yet another vasculitic syndrome, are most probably a secondary manifestation of endothelial damage. The disturbances, however, may well be of importance in extending the primary microvascular insult.

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Effects of posture and spinal bracing on respiratory function in neuromuscular disease

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SUMMARY Effects of posture and spinal bracing on lung function were studied in 40 children with neuromusclar disease, 20 of whom had scoliosis and were non-ambulant. Change from sitting to supine position had little effect on lung function in ambulant children, but caused a significant 12% reduction in forced vital capacity in a group of 16 non-ambulant children with scoliosis, suggesting diaphragmatic weakness in some. Spinal bracing, using a rigid supporting jacket, resulted in a significant reduction in mean vital capacity of 22%. The degree of impairment in forced vital capacity was proportional to the severity of the scoliosis (as measured by the Cobb's angle), to the amount of correction achieved by the brace, and to the degree of diaphragmatic weakness. Spinal bracing in a child with established severe scoliosis causes appreciable respiratory impairment, and this may explain why it is less likely to be tolerated than early prophylactic bracing.

Muscle disease in children is commonly associated with impairment of respiratory function.[1–5] One of the earliest changes is reduction in vital capacity due to weakness of the muscles of the chest wall or diaphragm, or both. Later there may be a progressive fall in pulmonary compliance due to microatelectasis,[3 5] and reduced compliance of the chest wall due to drooping of the ribs,[1] muscle fibrosis, and ankylosis of the joints. Scoliosis occurs in many patients with muscle disease, and it contributes to poor lung function by causing a further reduction in vital capacity and ventilation-perfusion mismatch.[6]

Studies in adults with diaphragmatic weakness have shown that the fall in vital capacity from the erect to the supine position is a good indicator of the degree of diaphragmatic weakness.[7] Similar changes occur in childhood (personal observation), although there are no published data. The effect of spinal bracing on lung function is important because any impairment of lung function due to bracing may affect the child's ability to tolerate the jacket. A previous study of children with idiopathic scoliosis showed that wearing a Milwaukee brace had no effect on vital capacity, but caused significant reduction in maximal voluntary ventilation.[8] The purpose of the present study was to determine why some children are unable to tolerate spinal bracing. We used the effect of posture as a measure of diaphragmatic function, and studied the effects of spinal bracing on lung function and the relation with the severity of the scoliosis.

Patients and methods

We studied 40 children with muscle weakness caused by a variety of diseases. They were divided into two groups according to functional status (Table 1). Group 1 comprised 20 ambulant children without scoliosis. The 20 children in group 2 were all non-ambulant and had scoliosis. Sixteen of these children wore a rigid lightweight polypropylene supporting brace to control their scoliosis. The children were accustomed to their brace, which was worn for at least six hours each day, but not at night. The degree of scoliosis was assessed both in and out of the brace by measurements of Cobb's angle[9] using radiographs taken in the sitting position. The functional status of the children was assessed using the Vignos score,[10] with increasing disability indicated on a scale from 1 to 9. According to this score, a child with a score of over 3 will be unable to climb stairs, and ambulation is lost at a score of over 7.

The lung function tests used were peak expiratory flow rate, using a Wright Peak Flow meter (Airmed), and spirometry (Ohio Electronic Spirometer) to determine forced vital capacity and forced

Table 1 *Clinical details of subjects in groups 1 (ambulant, no scoliosis) and 2 (non-ambulant plus scoliosis)*

	Duchenne muscular dystrophy	*Limb girdle dystrophy*	*Congenital muscular dystrophy*	*Spinal muscular atrophy*	*Other*
Group 1 (n=20)	5	5	3	2	5
Group 2					
(Posture study: n=15)	10	0	2	3	0
(Jacket study: n=16)	11	0	2	3	0

expiratory volume in one second (FEV_1). The best of three measurements was recorded for each test. None of the children had asthma or recurrent aspiration, and no child had any evidence of respiratory infection within six weeks of testing.

The children in group 1 were tested standing, sitting, and supine. Fifteen of the children in group 2 performed the test, sitting, and supine: they were unable to stand. Sixteen of the group 2 children were tested with and without their spinal jacket in the sitting position. Eleven children in group 2 took part in both the posture and the jacket study.

Predicted normal values were based on armspan.[11] Changes with posture or with and without jacket were assessed by paired Student's *t* tests. The mean within patient coefficient of variation of the tests was 4·6% for forced vital capacity, 7·1% for FEV_1, and 6·2% for peak expiratory flow rate.

Results

Both groups showed the expected impairment in forced vital capacity, FEV_1, and peak expiratory flow compared with predicted values (Tables 2, 3, and 4). There was a reduction in forced vital capacity expressed as a percentage of predicted values with increasing functional disability measured by the Vignos score (r=0·64, P<0·001, Fig. 1).

Posture had a significant effect on lung function. In group 1, mean forced vital capacity fell by 6% from sitting to supine positions (P<0·05, Table 2), but there were no significant changes in FEV_1 or expiratory flow. The children in group 2, however, showed highly significant impairment in all parameters of lung function from sitting to supine positions (P<0·01, Table 3). In four boys with Duchenne muscular dystrophy, forced vital capacity fell by more than 20% from the initial values in the sitting position, with a mean reduction of 12% for the group 2 as a whole (P<0·001). Mean FEV_1 fell by 12%, and mean peak expiratory flow fell by 14% from sitting to supine positions (Table 3).

The effect of spinal bracing on lung function was tested in 16 children in group 2. Wearing a jacket

Table 2 *Effect of posture on lung function in group 1 (20 ambulant children with no scoliosis). Values are mean (SD): figures in italics are mean % predicted*

	Forced vital capacity	*FEV_1*	*Peak expiratory flow rate (l/min)*
Standing	1·48 (0·52) *66*	1·38 (0·52) *70*	202 (83) *73*
Supine	1·40 (0·59) *63*	1·29 (0·54) *65*	193 (72) *70*
Sitting	1·50 (0·58)* *66*	1·37 (0·52) *68*	204 (19)* *74*

*Significantly different from supine value (P<0·05).
FEV_1=forced expiratory volume in one second.

Table 3 *Effect of posture in group 2 (20 non-ambulant children with scoliosis). Values are mean (SD): figures in italics are mean % predicted*

	Forced vital capacity	*FEV_1*	*Peak expiratory flow rate (l/min)*
Sitting	1·10 (0·51) *42*	0·98 (0·45) *43*	172 (72) *54*
Supine	0·97 (0·48) *38*	0·85 (0·44) *39*	148 (67) *48*
	t=4·38	t=3·26	t=4·57
	P<0·005	P<0·01	P<0·001

FEV_1=forced expiratory volume in one second.

Table 4 *Effect of brace in group 2 (16 non-ambulant children with scoliosis). Values are mean (SD): Values in brackets % predicted*

	Forced vital capacity	*FEV_1*	*Peak expiratory flow rate (l/min)*
Brace on	0·73 (0·43) *28*	0·63 (0·38) *28*	144 (68) *51*
Brace off	0·94 (0·58) *36*	0·80 (0·53) *36*	158 (83) *52*
	t=4·11	t=3·41	t=1·25
	P<0·01	P<0·01	ns

FEV_1=forced expiratory volume in one second.

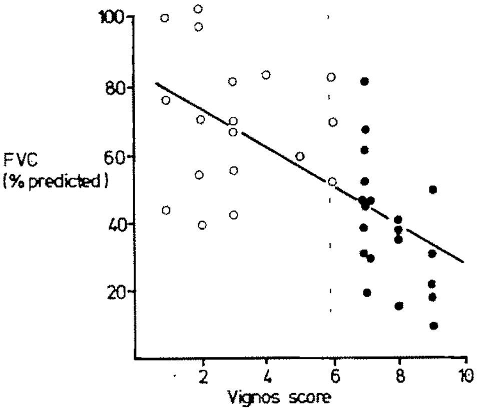

Fig. 1 *Relation between Vignos score and forced vital capacity (FVC) (% of value predicted from arm span).* Open circles group 1, closed circles group 2 patients. $r=0{\cdot}64$, $P<0{\cdot}001$.

caused a mean reduction in forced vital capacity of 22% ($P<0{\cdot}01$, Table 4), seven patients showing impairment of greater than 25%. The impairment in force vital capacity was related to the angle of scoliosis ($r=0{\cdot}5$, $P<0{\cdot}05$) and to the degree of improvement due to bracing ($r=0{\cdot}5$, $P<0{\cdot}05$, Fig. 2). The two children with the greatest impairment in forced vital capacity as a result of bracing both had severe Duchenne muscular dystrophy. They achieved considerable improvement in Cobb's angle with the brace but unfortunately this was at the cost of considerable restriction in lung volume. Furthermore, of the four boys with Duchenne muscular dystrophy who showed the greatest impairment in forced vital capacity when lying supine (suggesting severe diaphragmatic weakness), one was unable to tolerate a brace and the remainder showed severe restriction in forced vital capacity as a result of bracing. Mean FEV_1 fell by 21% as a result of bracing ($P<0{\cdot}01$, Table 4), but overall there were no significant effects on peak expiratory flow rate: in four patients the peak flow fell by more than 25% when wearing a jacket, but surprisingly, in three patients the peak flow improved by more than 25% in the brace, despite significant impairment in forced vital capacity.

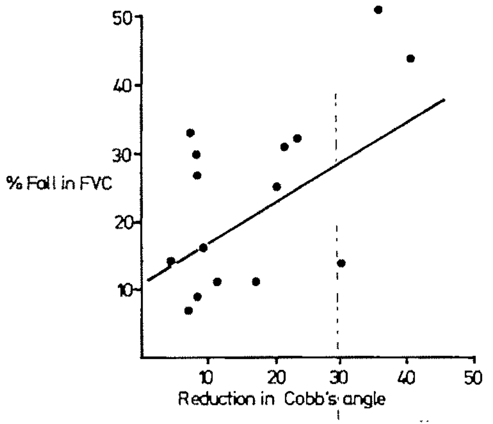

Fig. 2 *Relation between reduction in Cobb's angle due to the brace, and the fall in forced vital capacity (FVC) (% of baseline value) due to the brace.* $r=0{\cdot}5$, $P<0{\cdot}05$.

Discussion

We have shown that in severely weak patients, lung function may be significantly impaired in the supine position; furthermore, wearing a rigid supporting jacket for scoliosis causes further restriction in lung volume.

Posture has an effect on lung function in normal adults[12] with a fall of approximately 5% from erect to supine but we have been unable to find any published data for children. Twenty normal schoolchildren aged 6 to 17 years, however, studied at this hospital (Reynolds, 1979, unpublished data) showed a mean reduction in forced vital capacity of 4·8% from standing to supine positions ($P<0{\cdot}02$). All of the children in group 1 had definite muscle weakness, but the 6% fall in forced vital capacity from sitting to supine hardly differs from the normal population. The children in group 2, however, were weaker and had the additional disadvantage of scoliosis. In this group the mean fall in forced vital capacity from sitting to supine was 12%. Four boys with Duchenne muscular dystrophy showed reductions from 22 to 29%, suggesting a significant degree of diaphragmatic weakness. Three of these boys showed severe restriction in forced vital capacity as a result of bracing, and the fourth was completely unable to tolerate a brace.

It was surprising to find that three of the children with substantial impairment in forced vital capacity when supine actually improved their peak expiratory flow by 26 to 63% when wearing a brace. It is possible that these children might have learned to make use of the splinting effect of the brace on the abdomen and could thus improve their peak flow and also improve their capacity to clear secretions or cough.

Spinal bracing using rigid jackets is an important stage in the management of scoliosis, since there is rapid progression if left untreated, particularly in children with muscle weakness. Children with severe scoliosis, however, are usually reluctant to wear a brace. We have shown that spinal bracing for severe scoliosis results in a considerable reduction in forced vital capacity, and this may contribute to difficulty in tolerating the brace, particularly as lung function is already seriously impaired by weakness of the intercostal muscles and diaphragm. The reduction in forced vital capacity due to bracing was proportional to the angle of the scoliosis and the degree of correction achieved by the brace, and this would explain why early prophylactic bracing is more likely to be tolerated, since the jacket has little effect on lung function when the scoliosis is mild.

Children with muscle disease often need spinal surgery despite bracing. Operations such as the Dwyer procedure or Harrington instrumentation may require prolonged immobilisation in the supine position, which would be extremely hazardous in a child with severe diaphragmatic weakness. In such cases the newer Luque procedure[13] may be preferable, since earlier mobilisation is possible after surgery. Regular assessment of lung function using simple spirometry can give valuable information about the effects of bracing and about diaphragmatic function. The results may help to predict which children will be able to tolerate spinal bracing, and to decide on the timing of spinal surgery.

We thank Dr Debbie Hodes and Miss Caroline Dixon for their help with this project.

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Interleukin-1 in malnutrition

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SUMMARY The effect of malnutrition on the in vitro production of interleukin-1 by lipopolysaccharide stimulated circulating monocytes has been investigated in children suffering from kwashiorkor and marasmus. The interleukin-1 activity was significantly lower in children with severe malnutrition. Furthermore, macrophages from children with kwashiorkor produced factors that suppressed mouse thymocyte proliferation. These observations show a significant impairment of macrophage function and provide a mechanism for the suppression of cellular immunity in malnutrition.

Recent advances in immunology have highlighted the role of macrophages in resistance to infection. In vitro studies have shown that macrophage derived factors can substitute the parent cell in supporting T lymphocyte functions.[1] The antigen specific activation of T cells is dependent upon two distinct signals from macrophages. The Ia$^+$ macrophages present antigen to T cells in an immunogenic form that constitutes the first signal for T cell activation. Lymphocyte activation factor, which has been designated interleukin-1,[2] provides a maturational signal to antigen or mitogen primed T lymphocytes,[3] and thus leads to the elaboration of interleukin-2, which is necessary for the amplification of the cell mediated immune response.

Several clinical studies have shown that severe protein energy malnutrition adversely effects cell mediated immune responses.[4 5] The effect of severe malnutrition on the functional state of macrophages, however, has not been established. Therefore, we have tested in vitro interleukin-1 activity of macrophages in children suffering from severe protein energy malnutrition.

Subjects and methods

Eleven children aged between 2 and 5 years suffering from severe protein energy malnutrition were investigated. These children were admitted to the children's nutrition ward of Niloufer Hospital for treatment of kwashiorkor or marasmus. Five out of the 11 children investigated had kwashiorkor with severe growth retardation, oedema, and mental changes. Six children had marasmus with wasting and severe growth retardation. Children with overt infections were excluded from the study. Age matched, well nourished children were selected as controls, based on their weight/age.[6]

The general procedures for isolation of macrophages and assay of interleukin-1 have been described by Blyden and Handschumacher.[7] Ten ml heparinised (4 U/ml) blood was collected from each child. Parental consent was obtained.

Mononuclear cells were isolated on Ficoll Paque.[8] The mononuclear cell layer was washed twice with phosphate buffered saline. The cells were aliquoted into sterile petri dishes containing 1 ml Rosewell Park Memorial Institute medium (RPMI) with 10% fetal calf serum (FCS). After incubation for one and a half hours at 37°C the supernatant fluid containing non-adherent cells was discarded, and the adherent cells were washed twice with the same medium.

Production of interleukin-1. Twenty μg lipopolysaccharide/ml (Difco) was added to each petri dish containing adherent cells in 1 ml RPMI containing 1% FCS. To establish the inhibitory effect of macrophage derived prostaglandins on production of interleukin-1,[9] indomethacin (Sigma) was added at a final concentration of 7 μg/ml to one of the petri dishes and incubated at 37°C for 24 hours. The supernatant was collected and was centrifuged at 1000 rpm for five minutes to remove any particulate material and then frozen in a volume of 1 ml each. The adherent cells were dislodged from the plastic surface using 1% trypsin and were suspended in a volume of 1 ml RPMI containing 1% FCS. The cell count was determined in a haemocytometer. The cells were washed twice using the same medium and then disrupted by repeated freezing and thawing in a methanol bath, followed by treatment with a polytron homogeniser for three minutes at maximum speed. The cell lysate thus obtained was centrifuged at [illegible]000 rpm for five minutes to remove the particulate material and was frozen in a 1 ml volume for storage. Preliminary experiments determining interleukin-1 activity from this material indicated that cell disruption was complete.

Assay of interleukin-1. Thymocytes obtained from 4–6 week old albino Swiss inbred mice were used as the target cells. Animals were killed by cervical dislocation and the thymus gland removed. A thymocyte suspension was prepared by gently teasing the thymus gland in cold Hanks's balanced salt solution. Thymocytes were suspended in RPMI medium with 10% FCS layered in petri dishes and incubated at 37°C for one and a half hours to remove adherent cells. The supernatant fluid was centrifuged at 10 000 rpm for five minutes and the cells resuspended in RPMI containing 1% FCS. The cell count was adjusted to 2×10^6 cells/0·1 ml. Interleukin-1 samples were assayed in triplicate by the addition of 0·1 ml of the sample obtained from the crude supernatant lysate, prepared in serial dilutions ranging from 1:10 to 1:320. Interleukin-1 activity was separately tested in supernatant and lysate obtained from macrophages cultured with and without indomethacin. In all these assays, the ability of interleukin-1 to potentiate the thymocyte responsiveness to phytohaemagglutinin was measured. The test material was added in a volume of 0·1 ml with 0·03% phytohaemagglutinin (Burroughs-Wellcome) to the thymocyte culture containing 2×10^6 cells in 3 ml RPMI with 1% FCS. Thymocyte cultures stimulated with phytohaemagglutinin alone served as controls. ^{3}H Thymidine incorporation into DNA was measured by the addition of 74 kBq (2 μCi) of tritiated thymidine at 72 hours. Twenty four hours later the cultures were harvested and placed in toluene based scintillation fluid and the radioactivity measured in a liquid scintillation counter. Interleukin-1 activity was expressed as the difference of mean (SE) counts per minute between the test culture and the control cultures in appropriate dilutions. A representative dose response curve is given in Figure 1 to indicate the log linear relation between the decrease in thymidine incorporation with increasing dilution of the test material.

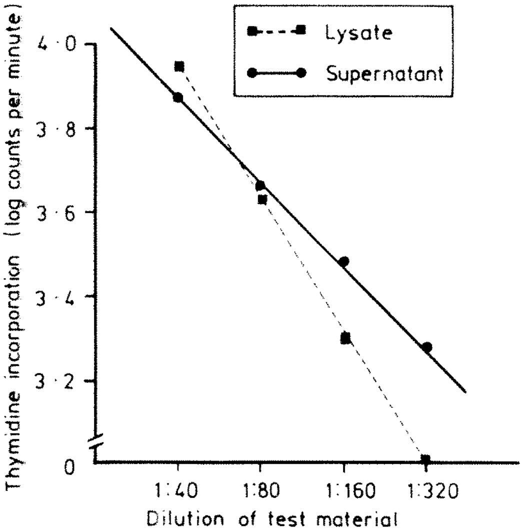

Fig. 1 *Dose response curve indicating the relation between decreasing thymidine incorporation and increasing dilution of the test material.*

Results

The numbers of macrophages recovered from the peripheral blood ranged from $4–6\times10^6$ in both controls and malnourished children. The total interleukin-1 activity obtained by pooling the activity in supernatant (extracellular activity) and cell lysate (intracellular activity) in corresponding dilutions was significantly higher in culture systems with indomethacin compared with those without (Fig. 2).

The interleukin-1 activity was found to be distributed almost equally in the extracellular and intracellular fractions in normal children (Fig. 3). The total interleukin-1 activity in normal children was found to be significantly higher than in children with marasmus or kwashiorkor (Fig. 4). In children with marasmus the intracellular and extracellular activities were found to be significantly lower than the

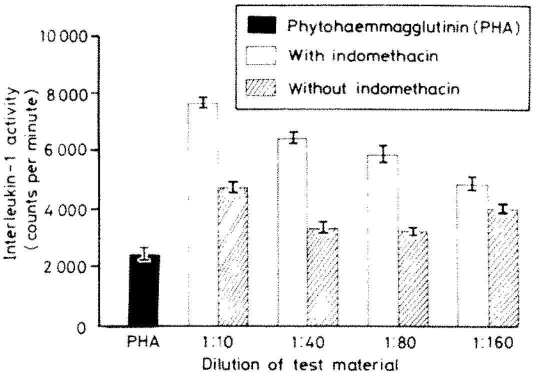

Fig. 2 *Effect of indomethacin on interleukin-1 activity.*

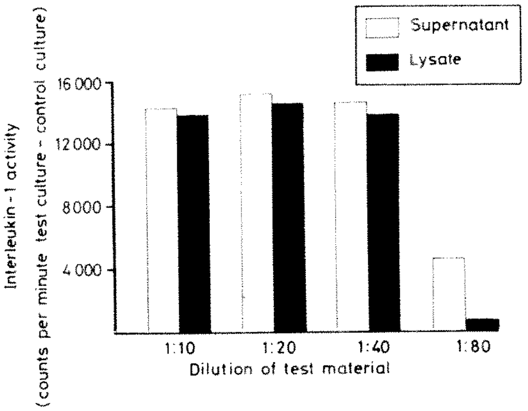

Fig. 3 *Intracellular and extracellular interleukin-1 activity in normal children.*

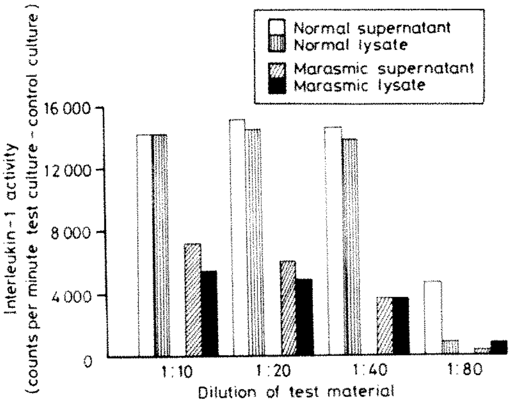

Fig. 5 *Intracellular and extracellular interleukin-1 activity in children with marasmus.*

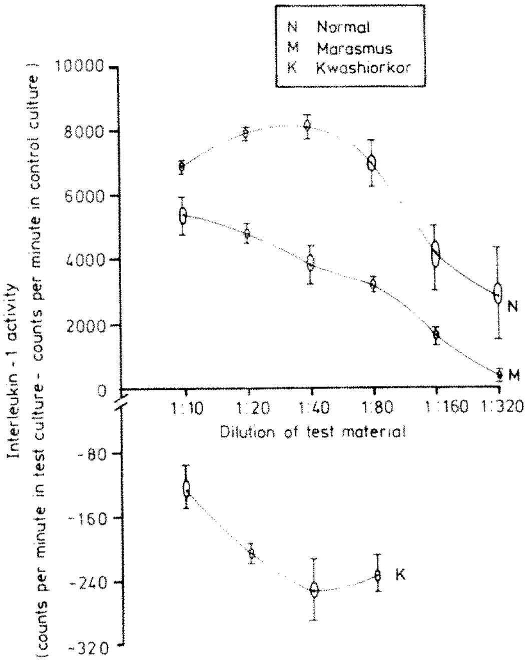

Fig. 4 *Total interleukin-1 activity in malnutrition.*

corresponding activities in normal children (Fig. 5). In children suffering from kwashiorkor, however, the thymidine incorporation in cultures with macrophage material was less than the incorporation observed with phytohaemagglutinin alone; this accounts for the negative figures (Fig. 4).

Discussion

It is well established that macrophages play a crucial though non-specific role in cellular immune responses. Ia^+ macrophages are involved in the processing and presentation of antigen to specific T lymphocytes.[3] Further, they are involved in the elaboration of interleukin-1, which provides a maturational signal to the antigen primed T lymphocyte.

The adverse effects of malnutrition on cell mediated immunity are thought to be due to defective T cell function. Experimental studies determining the effect of malnutrition on macrophage function are few and controversial.[10 11] Recent clinical studies from this laboratory have shown that mobilisation of monocytes in vivo to a site of injury is impaired in malnourished children.[12] The decreased opsonic activity of the serum due to lowered complement concentrations in such children might impair the phagocytic capacity in vivo.[13]

The present study confirms that macrophage derived interleukin-1 activity is present in the cell lysate as well as in the supernatant.[14] This finding strengthens the importance of estimating intracellular and extracellular interleukin-1 activity separately. The activity of interleukin-1 was found to be almost equal in the intracellular and extracellular compartments in normals. Gery, however, reported higher intracellular interleukin-1 activity from lipopolysaccharide stimulated macrophage;[14] the explanation for this difference is not clear.

The suppression of interleukin-1 in culture systems without indomethacin and restoration of interleukin-1 activity with indomethacin confirms earlier observations that macrophage derived prostaglandins are involved in suppression of interleukin-1 activity.[9]

In the present study decreased interleukin-1 activity is shown in patients with severe protein energy malnutrition. As both intracellular and extracellular activity is lowered in children with marasmus, the intracellular production of interleukin-1 is probably compromised. In addition, the significant suppression of phytohaemagglutinin induced thymocyte responses in patients with kwashiorkor suggests the presence of a macrophage derived suppressor factor(s).

The reduced interleukin-1 activity and the possible production of a suppressor factor provide a mechanism for the defect in cell mediated immune responses in severely malnourished children.

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Plasma concentrations of clonazepam after single rectal administration

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SUMMARY Clonazepam was administered rectally to six children aged 1·4 to 4·7 years in a dose of 0·05 mg/kg and to five children aged 1·4 to 4·1 years in a dose of 0·1 mg/kg. Plasma concentrations indicate that it is rapidly absorbed, and it may therefore be an alternative to rectal administration of diazepam in continuing convulsions.

Diazepam is considered to be the drug of choice for continuing convulsions.[1] Used rectally, it is a safe and rapidly effective treatment that can be administered easily and conveniently by paediatric residents, general practitioners, nurses, and parents.[1,2] It may, however, cause respiratory depression,[3] and convulsions sometimes recur after initial suppression.[3,4]

Intravenously administered clonazepam is effective in all forms of continuing convulsions[5,6] and has a longer duration of action than diazepam.[6] Respiratory depression seems to occur much less commonly than with diazepam. Blood concentrations after rectal administration in adults are similar to those achieved after intravenous administration,[7] but the rate and extent of absorption of rectally administered clonazepam in children is not known.

We have determined the plasma concentration time profiles after rectal administration of two different doses.

Methods

Eleven children (nine boys and two girls) were included in the study. Their ages ranged from 1·4 to 4·7 years (Table). They were all in good general health but had previously had convulsions associated with fever. One child was taking sodium valproate and another carbamazepine regularly. The test doses were given to confirm adequacy of absorption and suitability for individual home use. Ethical approval from the local district research ethical committee had been obtained.

The commercial appropriately diluted intravenous preparation Rivotril (Roche, UK) was administered directly into the rectum through 1 ml

Table *Plasma clonazepam concentration in 11 children after single rectal dose administration (ng/ml)*

Case no	*Age (yrs)*	*Other drugs*	*Dose (mg/kg)*	*Time after administration*										
				Minutes							*Hours*			
				0	*2*	*4*	*7*	*10*	*20*	*30*	*1*	*2*	*4*	*12*
1	4·6		0·044	—	—	—	—	—	—	—	—	—	—	—
2	4·7		0·046	—	—	—	—	—	2·8	—	—	—	—	—
3	4·6		0·050	—	—	—	1·0	—	1·1	2·1	1·4	1·7	1·3	—
4	1·4		0·050	—	—	—	—	—	5·7	7·5	11·0	7·4	10·4	—
5	2·3	Carbamazepine	0·040	—	—	—	—	8·5	8·2	12·0	8·5	9·5	4·7	—
6	1·4		0·050	—	—	—	3·4	4·5	10·7	11·5	7·2	7·2	5·8	3·2
7	2·0		0·091	—	—	—	7·1	28·0	23·3	11·7	10·5	12·3	7·3	5·3
8	3·3		0·099	—	—	—	7·1	85·8*	38·6	27·1	40·5	23·7	24·3	18·7
9	1·4		0·095	—	—	—	5·0	11·1	17·9	18·4	17·5	12·3	13·4	8·0
10	3·1	Sodium valproate	0·100	—	—	—	—	11·2	18·8	25·0	23·4	21·7	20·1	11·8
11	4·1		0·100	—	—	—	7·3	13·2	24·9	26·6	37·6	39·0	18·3	20·2

—=Undetectable concentration.
*Disproportionately high concentration omitted from peak results and Figure.

syringes inserted 3 cm through the anal sphincter. Six children were given 0·05 mg/kg, and five children were given 0·1 mg/kg as bolus injections. Venous blood samples were obtained through an indwelling heparinised cannula before and at two, four, seven, 10, 20, and 30 minutes and one, two, four, and 12 hours after administration.

The clonazepam concentrations in children given 0·5 mg/kg doses were measured by a modification of the method using gas chromatography with electron capture detection reported by de Silva and Bekersley.[8] The overall precision of these measurements was ±14·3%, and concentrations of 1 ng/ml could be determined with a coefficient variation of ±28%. The concentrations in children given 0·1 mg/kg were measured by the capillary gas chromatography method reported by de Boer *et al.*[9] The coefficient of variation of this assay was ±15%.

Results

The Table shows the clonazepam concentrations for each dose. One child (case 1) in the group given 0·05 mg/kg did not achieve detectable concentrations. Two others (cases 2 and 3) failed to achieve concentrations above the lower limit for detection in the group given 0·1 mg/kg. The 10 minute concentration in case 8 was disproportionately high and out of line with the remaining profile. It has been omitted from the following results. Peak concentrations in children given 0·05 mg/kg ranged from 2·8 to 12·0 ng/ml and occurred 20–60 minutes after rectal administration. Peaks of 18·4–40·5 ng/ml occurred between 10 minutes and two hours in those given 0·1 mg/kg. No child in either dosage group had detectable concentrations before seven minutes.

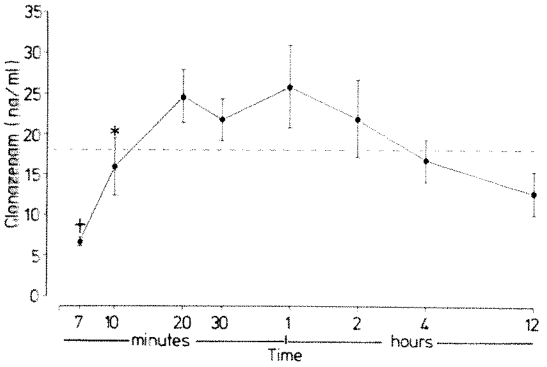

Figure *Plasma clonazepam concentrations (mean (SE)) in five children after rectal administration of 0·1 mg/kg dose (– – –=suggested 'therapeutic threshold').*

*One high concentration excluded.
†Omission of one sample with undetectable concentration.

The Figure shows the mean (SE) concentration time curve for children given 0·1 mg/kg.

All children given 0·1 mg/kg became drowsy, fell asleep within 20 minutes, and remained so for over three hours. Three (cases 8, 10, and 11) remained ataxic and incoordinated at four hours.

Discussion

Peak concentrations between 10 minutes and two hours after rectal administration of solution suggest that clonazepam is rapidly absorbed from the rectum. These concentrations occurred slightly later, however, than those reported for diazepam in children.[10 11] Peak concentration times after intravenous injection have not been reported in children of this age, but it must be assumed that the peaks after rectal administration occur later.

Blood concentrations of clonazepam necessary to stop continuing convulsions are not known. Ståhl *et al* reported that epileptogenic discharges on electroencephalogram were noticeably reduced or abolished for varying periods in four children given clonazepam intravenously; peak concentrations at these times ranged from 7 to 11 ng/ml.[12] Congdon and Forsythe found no recurrence of convulsions in children with concentrations above 17·7 ng/ml.[6] In adults clonazepam concentrations up to 36·8 ng/ml were obtained in volunteers given 2 mg intravenously. This dose is twice that which usually stops convulsions in this age group. A therapeutic concentration threshold of 18 mg/ml might therefore be suggested, although this may be higher than necessary and subject to wide interindividual variation. No child given 0·05 mg/kg achieved this concentration, but the value was exceeded within 20 minutes in all children given the higher dose. Slightly lower concentrations achieved by all children within 10 minutes may well be effective.

None of the children in this study showed signs of respiratory depression. This has been reported considerably more often after the use of diazepam intravenously, although this may reflect the more common use of this drug. Other adverse effects did occur, however, in all children in the higher dosage group. They had muscular incoordination, ataxia, and sleepiness with onset within 20 minutes of administration and a duration of at least three hours. The three patients who remained ataxic at four hours were not so one hour later, although all remained drowsy. Although these effects occurred when plasma concentrations were highest and were only present when concentrations exceeded 18 ng/ml, except in case 11 who was not ataxic with a concentration of 20·2 ng/ml at 12 hours, there may be no clear relation between such adverse effects and drug concentrations. Similar concentrations produced such effects in only half the children in the series reported by Dreifuss *et al.*[13] Whether the incidence of such effects after the use of clonazepam to stop convulsions represents a major disadvantage is not clear.

If clonazepam is the drug of choice for continuing convulsions[14] then the facility for a convenient and rapidly effective therapeutic approach offered by rectal administration would be as important for clonazepam as has been shown to be the case in practice for diazepam. These results suggest that a dose of 0·1 mg/kg clonazepam administered rectally to young children may be expected to produce a rapidly effective anticonvulsant effect. Further work is necessary to confirm its rapid absorption, its usefulness as an effective treatment, and to develop convenient means of administration along lines presently offered by the availability of rectal tubes containing diazepam (Stesolid).

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Short reports

Congenital hypothyroidism missed on screening

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SUMMARY Three patients with congenital hypothyroidism missed on routine screening due to normal low thyrotrophin concentrations in the neonatal period presented in later childhood. Clinicians should remain aware of hypothyroidism as a cause of morbidity in early childhood despite a national screening programme.

Screening for congenital hypothyroidism started in Northern Ireland in January 1980. Over the last five complete years 137 612 infants have been screened and 33 patients diagnosed hypothyroid. The annual incidence of one in 4170 live births is similar to the experience in other European centres.[1] During the same period, three patients with normal screening tests taken between seven and 10 days after birth were diagnosed clinically hypothyroid at 7–33 months of age. These patients were born in 1981 when the screening policy was to measure whole blood thyroxine concentrations in duplicate on all samples and follow up the lowest 20% with an estimation of whole blood thyrotrophin concentrations in duplicate. Patients with thyrotrophin concentrations $\geq$25 mU/l were recalled for examination and further investigation. The screening method was subsequently changed to measuring thyrotrophin concentrations alone on all patients, a practice followed by most centres in the United Kingdom, as it is generally agreed that thyrotrophin screening will identify more patients with hypothyroidism than thyroxine screening.[2] However, the following case reports of patients missed on neonatal screening have important implications when a raised thyrotrophin concentration is used as the only indication for recall.

Case reports

The initial neonatal screening results are summarised in Table 1. All three patients had thyroxine concentrations in the lowest 20% range, so thyrotrophin estimations were performed in duplicate from the same whole blood sample. As the thyrotrophin concentration was not raised no further action was taken.

All three patients, born at term by normal delivery, had symptoms from early infancy consistent with hypothyroidism, most notably prolonged jaundice, feeding difficulty, and lethargy. Diagnosis was delayed until 7–33 months of age, by which time obvious hypothyroid facies, short stature, delayed developmental milestones, and delayed bone age were present. Thyroxine replacement therapy was started with dramatic clinical improvement in each case.

When patients were over 3 years old they were assessed by standard intelligence tests. After withdrawing thyroxine for a short period a radioisotope scan (^{123}I) was performed. These results are summarised in Table 2. None of the patients had circulating thyroid antibodies, and their mothers had no evidence of thyroid or autoimmune disease.

Table 1 *Neonatal screening results and age at clinical presentation*

Case No	*Sex*	*Age (days)*	*Thyroxine (nmol/l)*	*Thyrotrophin (mU/l)*	*Age at diagnosis (months)*	*Bone age at diagnosis (Greulich and Pyle)*
1	M	7	41	<25	7	38 weeks' gestation
2	F	8	38	<25	33	6 months
3	M	10	53	<25	33	6 months

Conversion: SI to traditional units—Thyroxine: 1 nmol/l≈77·7 µg/100 ml.

Table 2 *Results of intelligence tests and effects of thyroxine withdrawal*

Case No	*Age (years)*	*Stanford Binet intelligence scale*	*Duration of thyroxine withdrawal (days)*	*Serum thyroxine (nmol/l)*	*Serum thyrotrophin (mU/l)*	^{125}*I Scan*
1	3·6	89	24	16	87	Athyreosis
2	3·3	95	37	11	380	Hypoplastic
3	3·3	100	37	15	390	Ectopic

Conversion: SI to traditional units—Thyroxine: 1 nmol/l=77·7 μg/100 ml.

Discussion

Three patients with congenital hypothyroidism are presented who were not diagnosed by routine neonatal thyrotrophin screening despite symptoms consistent with that diagnosis from birth. The most severely affected patient both clinically and on intelligence testing on follow up was found on subsequent investigation to have no functioning thyroid tissue on radioisotope scan. The two patients both diagnosed at 33 months of age with hypoplastic or ectopic glands showed dramatic physical and intellectual improvement with thyroxine replacement therapy. This more prolonged presentation with less morbidity is consistent with some endogenous thyroxine production during the critical period of brain growth in infancy and agrees with a previous report of higher intelligence quotients in patients diagnosed at 2 years compared with those diagnosed between 6 and 9 months of age.[3]

Why were low thyroxine concentrations on screening not associated with rises in thyrotrophin concentrations in the neonatal period? All screening procedures are subject to human and laboratory error, which are difficult to exclude retrospectively.[4] Unfortunately, the original samples were not available for retesting as four tests of thyroid function (thyroxine and thyrotrophin in duplicate) had been performed on the original dried blood spots. The sample still remaining had been autoclaved as a routine procedure to denature haemoglobin before phenylalanine screening and was therefore unsuitable for repeat estimation of thyrotrophin concentration. All samples, however, were measured in duplicate by reliable assays. No patient was preterm or breast fed, and no mother had evidence of thyroid disease. A normal increase in thyrotrophin concentrations was shown after withdrawal of treatment at 3 years of age. The probability remains that these patients had an abnormally slow rise in thyrotrophin concentrations after birth. Similar patients have been described and the suggestion made that the cause may be immaturity of the hypothalamic–pituitary–thyroid axis.[5]

The present hypothyroid screening policy, using thyrotrophin alone, adopted throughout most centres in Europe will not detect these patients unless a second screening test is routinely repeated after a few weeks. Alternatively, thyroxine concentrations could also be measured routinely on all samples and low thyroxine results followed or investigated. Either procedure would greatly increase the time and expense of screening and so is unlikely to be undertaken routinely. It is important, therefore, that clinicians continue to remain aware of hypothyroidism as a potential cause of illness in infants despite a national screening programme.

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Biliary scintigraphy with DISIDA

A simpler way of showing bile duct patency in suspected biliary atresia

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SUMMARY 99^{m}TC-diisopropyl iminodiacetic acid (DISIDA) scintigraphy after oral phenobarbitone treatment accurately indicated bile duct patency or obstruction in 28 of 32 (87%) infants, aged less than 12 weeks, with suspected biliary atresia.

This investigation is more rapid than and as accurate as the ^{131}I Rose-Bengal faecal excretion test.

Demonstration of bile duct patency using radionuclides is often an essential investigation in distinguishing extrahepatic biliary atresia from intrahepatic disease causing severe cholestasis. The improved results from portoenterostomy for biliary atresia, particularly if performed in the first 2 months of life,[1] together with the deleterious effect of inappropriate laparotomy and biliary surgery for infants with hepatic disease,[2] make early accurate diagnosis essential.

Difficulties with the ^{131}I Rose-Bengal faecal excretion test, which requires a 72 hour stool collection, have prompted consideration of new isotope excretion tests. Iminodiacetic acid (IDA) compounds are rapidly removed from the circulation by the liver and excreted in bile and, when labelled with ^{99m}technetium, the biliary-intestinal excretion may conveniently be shown with a gammacamera.

A new IDA compound, diisopropyl IDA (DISIDA) with improved lipid solubility allowing hepatic uptake at a high serum bilirubin concentration and with a shorter hepatobiliary transit time, has theoretical advantages over earlier IDA compounds, which often fail to distinguish biliary atresia from hepatic disease.[3] We report an assessment of the value of DISIDA scintigraphy in 50 consecutive infants investigated because of conjugated hyperbilirubinaemia in the first 12 weeks of life.

Patients and methods

All 50 infants were investigated for possible genetic, metabolic, infective, and structural causes of hepatobiliary disease. DISIDA scintigraphy was not carried out in 18 infants as they had either pigmented stools (13), α_1 antitrypsin deficiency (PiZ) previously diagnosed by phenotyping (four), or the presence of a choledochal cyst on ultrasound (one). DISIDA scintigraphy was performed in 32 infants in whom distinction between biliary atresia and hepatic disease was difficult. Of these, 21 subsequently had ^{131}I Rose-Bengal faecal excretion studies.

Radionuclide tests. In 32 infants 40 mBq (1 mCi) ^{99m}Tc-DISIDA was injected intravenously after a three day course of oral phenobarbitone (5 mg/kg/day). Imaging was carried out at five minute intervals for the first hour and then at hourly intervals for 10 hours or until radioactivity was seen in the intestines. If excretion was still not apparent imaging was repeated at 24 hours. In 21 infants 0·2 mBq (5 μCi) ^{131}I Rose-Bengal was injected intravenously. Stools were then collected for three consecutive days, taking care to avoid urinary contamination.

Results

Diagnoses and results of the radionuclide tests are shown in the Table. There was no biliary excretion of DISIDA in 23 infants. Biliary atresia was confirmed at laparotomy in 20 of these. In two infants liver biopsy specimens showed features of bile duct hypoplasia, and their subsequent course confirmed the diagnosis. The other child had histological features of biliary atresia, but laparotomy was not performed because of advanced liver disease with ascites. No post mortem was performed. There was delayed excretion of tracer at 24 hours in three cases: one had a bile duct plug diagnosed at laparotomy, one had α_1 antitrypsin deficiency, and one had severe familial neonatal hepatitis of unknown aetiology. Excretion of DISIDA was evident by three hours in six infants, one with α_1 antitrypsin deficiency and five with hepatic disease suggested by liver biopsy and confirmed by subsequent clearing of jaundice. ^{131}I Rose-Bengal faecal excretion was less than 10% in all 14 with biliary atresia and in four others with acholic stools, one of whom had α_1 antitrypsin deficiency (delayed excretion of DISIDA) and three with intrahepatic disease (one of whom had no excretion of DISIDA). Diagnostic accuracy was therefore 87% (28 out of 32) for DISIDA and 81% (17 out of 21) for Rose-Bengal.

Table *Diagnoses and results of the radionuclide tests in the 50 infants*

Diagnosis	*No*	*DISIDA*				*Rose-Bengal*		
		No excretion	*Rapid excretion*	*Delayed excretion*	*Not done*	*<10%*	*>10%*	*Not done*
Biliary atresia	21	20	0	0	1	14	0	7
Bile duct plug	1	0	0	1	0	0	0	1
α_1 Antitrypsin deficiency	6	0	1	1	4	1	0	5
Hepatic disease	22	3	5	1	13	3	3	16
Total	50	23	6	3	18	18	3	29

Discussion

A skilfully interpreted percutaneous liver biopsy specimen and ^{131}I Rose-Bengal faecal excretion test have been shown to discriminate between biliary atresia and hepatic disease once genetic disorders have been excluded.[3] Neither test alone is reliable. The use of ^{131}I as a tracer in infancy is not ideal as it is a beta emitter with a long half life, although the dose is very small. The test also involves collection of stools for three days, carefully avoiding urinary contamination that may invalidate the result. This study suggests that DISIDA scintigraphy after treatment with phenobarbitone is as accurate as the Rose-Bengal test. Whether it is necessary to use phenobarbitone is uncertain.[4 5] It was used in this study because five of seven infants with hepatic disease had no excretion of paraisopropyl IDA when tested without phenobarbitone but did excrete after treatment with phenobarbitone.[6]

DISIDA scintigraphy has the drawback that it is subjective, allowance having to be made for isotope in the kidneys and bladder, and time consuming. Assessment of hepatic uptake of DISIDA may increase diagnostic accuracy.[4 5] Nevertheless, when used in conjunction with ultrasonography, tests for infective and genetic causes of liver damage, and percutaneous liver biopsy DISIDA scintigraphy represents a considerable advance in distinguishing complete from partial cholestasis in early infancy.

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Splenunculectomy in thrombocytopenic purpura

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SUMMARY In six patients with thrombocytopenic purpura not cured by splenectomy platelets fell to $<150\times10^9$/l within six weeks of splenectomy. They 'failed to respond'. Two underwent splenunculectomy without improvement. Splenunculectomy offered little chance of improvement to published cases who failed to respond but may well be helpful after true relapse.

A small proportion of children with persisting idiopathic thrombocytopenic purpura are not cured by splenectomy.[1] It has long been postulated that enlarged accessory spleens may be responsible for recurrent thrombocytopenia in some splenectomised patients, and splenunculectomy has cured or improved several such patients.[2-5]

With this aim we reinvestigated seven patients who were not cured by splenectomy and offered splenunculectomy to those with persistent bruising in whom an accessory spleen was shown.

Methods

Platelets were labelled with ^{111}In-oxine under aseptic conditions. Eight MB$_q$ of labelled platelets were injected intravenously and anterior and posterior abdominal scintigraphs obtained at one hour and one, two, and three days with a gammacamera.

Patients

The seven patients were aged between 4 and 12 years (mean 8 years) at the onset of the purpura. Splenectomy was performed between one and four years (mean two years) after diagnosis. The response to splenectomy in the seven patients is shown in the Figure. Case 7 became thrombocytopenic and started bruising again at one year after splenectomy. Indium scans were obtained between two and 19 years (mean 10 years) after splenectomy. Enlarged accessory spleens were found in cases 1 to 4. Cases 3 and 4 underwent splenunculectomy. Neither was improved.

Discussion

The response to splenunculectomy in cases 3 and 4 was disappointing and caused us to review more critically the published reports. The role of splenunculectomy in patients with idiopathic thrombocytopenic purpura who have not been cured by splenectomy has been obscured by loose use of the term 'recurrent' and by widely differing interpretations of what constitutes a remission. For example, Wallace *et al* required a platelet count $>150\times10^9$/l at an unspecified time after splenectomy,[3] and Verheyden *et al*, in their survey of cases in the English reports, included two whose post splenectomy 'remissions' lasted only 12 and 30 days.[4]

In our experience some rise in the platelet count occurs in almost all children with idiopathic thrombocytopenic purpura immediately after splenectomy, but it is unlikely to be sustained unless the count exceeds 300×10^9/l in the first week.[1] It is also clear from the patients shown here that such a rise does not guarantee cure. We classified empirically those patients not cured by splenectomy whose counts fell below 150×10^9/l within six weeks, irrespective of their peak concentrations, as having

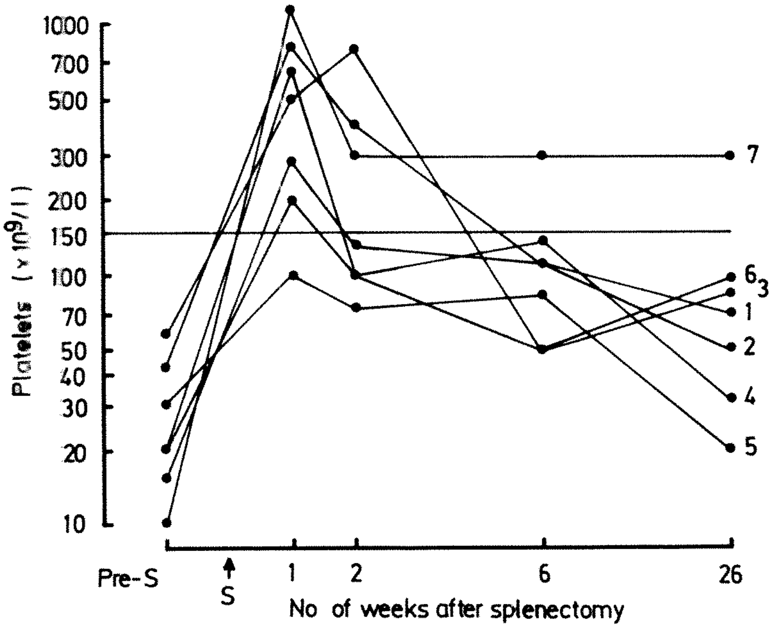

Figure *Platelet counts in the seven patients not cured by splenectomy.*
Pre-S=pre-splenectomy. S=splectomy.

idiopathic thrombocytopenic purpura that 'failed to respond' to splenectomy. Only case 7 could be considered to have a true relapse of the purpura, and he did not have an enlarged accessory spleen.

Despite clinicians' enthusiasm for removing accessory spleens, this operation has produced a remission in less than a third of cases presenting up to 1981.[3 4] Application of our criteria to these cases suggests that half of those with true relapses of idiopathic thrombocytopenic purpura responded while none who failed to respond to splenectomy did. To this latter group may now be added our own two patients. In 1981 Pawelski *et al*[5] described 12 patients with apparently true relapses of the purpura after splenectomy, all of whom were cured by splenunculectomy.[5]

Purpura that fail to respond to splenectomy should be distinguished from true post splenectomy relapses. This has not been the case in the past. Although the number of children not cured by splenectomy in our centre is small, we believe that criteria such as ours (platelets $<150\times10^9$/l within six weeks of splenectomy) may identify a group of patients very unlikely to respond to splenunculectomy. Patients who have had a true relapse of the purpura after apparently successful splenectomy in whom an enlarged accessory spleen is shown may well benefit from its removal.

The authors thank Miss J Gibson for meticulous record keeping and for plotting the platelet counts.

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Pancytopenia caused by iron-dextran

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SUMMARY Pancytopenia after intramuscular iron-dextran treatment occurred in an infant with Down's syndrome. Haematological abnormalities recurred on subsequent challenge. Positive migration inhibiting factor and mast cell degranulation tests support an allergic pathogenesis for the pancytopenia. These side effects have not been reported previously.

Severe, even fatal, allergic reactions are known to occur after parenteral administration of iron-dextran (Imferon). We describe a patient who developed thrombocytopenia, leucopenia, and haemolytic anaemia after intramuscular injection of iron-dextran. These haematological abnormalities recurred on subsequent challenge.

Case report

A 1 year old girl with Down's syndrome was admitted to our department. Blood count showed an iron deficiency anaemia with haemoglobin concentration 83 g/l, packed cell volume 0·28, mean corpuscular volume 71 fl, leucocytes 8×10^9/l (70% neutrophils, 12% band forms, 16% lymphocytes, 2% monocytes), and platelets 165×10^9/l. Serum iron concentration was 2·3 mM/l (12·7 μg%). Iron binding capacity was 55 mM/l (307 μg%). Intramuscular iron-dextran (30 mg/kg) was given in three divided doses over six days because of feeding problems and poor compliance. Ten days later the haemoglobin concentration rose to 98 g/l, and the reticulocyte count was 4·8%. The leucocyte count was $9\cdot7\times10^9$/l with normal differential count, and the platelet count was 180×10^9/l. She was discharged home but was readmitted to hospital one month later. Her blood count showed pancytopenia with haemoglobin concentrations 74 g/l, packed cell volume 0·24, mean corpuscular volume 85 fl, leucocytes $3\cdot3\times10^9$/l (49% neutrophils, 4% band forms, 43% lymphocytes, 2% monocytes, and 2% eosinophils), and platelets 50×10^9/l (Figure). Direct and indirect Coombs' tests were negative, her glucose-6-phosphate concentration was normal, and

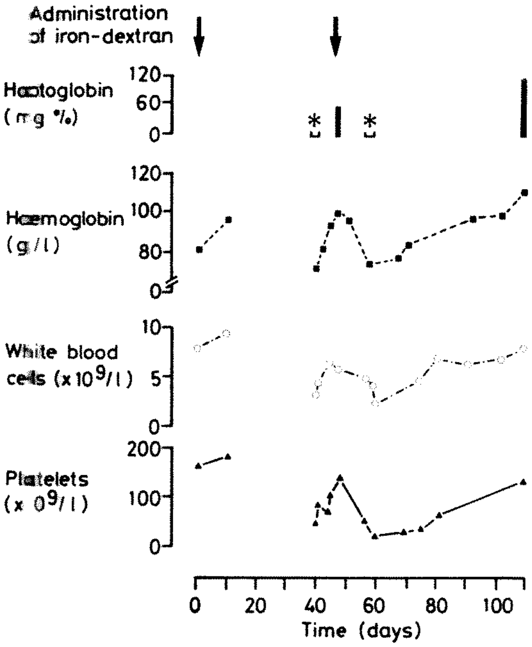

Figure *Haematological data after administration of iron-dextran (*undetectable concentration).*

her haptoglobin concentration was undetectable. Bone marrow aspirate showed normal reactive hypercellularity of all blood elements.

Serum concentrations of IgG, IgA, IgM, and C3 were 12·35 g/l, 0·67 g/l, 1·21 g/l, and 0·74 g/l, respectively. Antinuclear antibodies, rheumatoid factor, antithyroid, anti-parietal cell, antimitochondrial and anti-smooth muscle antibodies were all negative. Total lymphomononuclear counts ranged between $0\cdot3\times10^{9}$/l and $3\cdot08\times10^{9}$/l. B and T cell numbers could not be determined; the response to phytohaemagglutinin mitogen, however, was normal, whereas the response to pokeweed mitogen was reduced.

At this stage a challenge with a single dose of 10 mg/kg iron-dextran intramuscularly was performed after informed consent had been obtained from the parents. Two weeks later pancytopenia reappeared with haemoglobin 76 g/l, packed cell volume 0·26, mean corpuscular volume 100 fl, reticulocytes 10%, leucocytes $2\cdot8\times10^{9}$/l (53% neutrophils, 11% band forms, 26% lymphocytes, 6% monocytes, and 4% eosinophils), and platelets 22×10^{9}/l. The haptoglobin concentration dropped again to an undetectable level (Figure).

Tests with iron-dextran for the presence of a migration inhibition factor and mast cell degranulation were positive. Six weeks later the haemoglobin concentration rose spontaneously to 113 g/l, packed cell volume to 0·39, mean corpuscular volume to 103 fl, leucocytes to $8\cdot1\times10^{9}$/l, platelets to 140×10^{9}/l, and haptoglobin concentrations to 1·09 g/l (Figure).

Discussion

Many adverse reactions associated with the administration of parenteral iron-dextran preparations have been described.[1] Local reactions may include pain at the injection site, skin discoloration, and local inflammation. An association between intramuscular iron and subsequent development of soft tissue sarcoma has also been reported.[2] Adverse systemic reactions may be immediate or delayed and include headache, nausea, vomiting, muscle and joint pain, generalised lymphadenopathy, fever, bronchospasm, and anaphylactic reactions, which may be fatal.[1] The dextran component itself is known to cause immune complex mediated (type III) anaphylaxis in man.[3] Berliner *et al* described allergic non-thrombocytopenic purpura after intravenous administration of iron dextran (Imferon) with positive reaction of migration inhibition factor to this drug.[4] Haematological abnormalities after administration of iron were described, but a non-immune mechanism was suggested as the aetiology: Hamblin and Simmonds described neutropenia associated with treatment with iron and proposed a non-immune mechanism, where the stem cells are diverted from granulocyte production into erythrocyte production.[5] They alternatively suggested that the iron may have a direct toxic effect on the bone marrow. Fielding and Smith have shown non-immune haemolytic activity of an iron-dextran complex in an in vitro model.[6]

We emphasise that immunological disturbances are well recognised in Down's syndrome. Cellular immunity is impaired, as manifested by decreased number and function of peripheral T lymphocytes. There is usually an increase in the concentrations of serum IgG, IgA, and IgD with normal IgM. Cellular immunodeficiency is a known predisposing factor of autoimmunity, and may have contributed to the unusual adverse reaction to the drug in our patient.

Iron deficiency per se may affect immune competence. An additional factor behind the adverse reaction to iron-dextran in our patient may have been a defective host-defence mechanism induced by the iron deficiency itself.

Our patient developed thrombocytopenia, leucopenia (neutropenia and lymphopenia), and haemolytic anaemia after intramuscular administration of iron-dextran. These haematological abnormalities reappeared after a challenge with iron-dextran and were accompanied by positive migration inhibition factor and mast cell degranulation, suggesting hypersensitivity to this drug.

We thank Ella Livni, PhD, Clinical Laboratory, Beilinson Medical Center, who performed the migration inhibition factor and mass cell degranulation tests and Ms N Alon for her technical help.

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Phenobarbitone prophylaxis of intraventricular haemorrhage

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SUMMARY Thirty preterm infants (birthweight under 1500 g) were treated with phenobarbitone to examine its effectiveness in reducing the incidence of intraventricular haemorrhage (IVH), the control group comprising 28 infants. The treated group had 57% incidence of IVH and mortality of 13% compared with 68% and 14%, respectively, in controls.

Since barbiturates have been shown to have neuroprotective effects several reports have examined the effectiveness of phenobarbitone in the prevention of intraventricular haemorrhage (IVH) in preterm infants. The conflicting results obtained in these trials led us to re-evaluate this issue using the protocol of Donn *et al*, who showed that phenobarbitone reduced the incidence of IVH.[1]

Subjects and methods

We studied 58 preterm infants (birthweight less than 1500 g) who had no congenital malformations and whose mothers had not received phenobarbitone before their delivery. We randomly allocated these infants into control and treatment groups. The two groups were comparable with respect to birthweight, gestational age, race, sex, mode of delivery, and Apgar score. The control group (n=28, birthweight 1120 (SD 218) g) received supportive care only. The treatment group (n=30, birthweight 1119 (SD 264) g) received phenobarbitone for the first week of life, starting at less than 6 hours of age. We administered phenobarbitone in a loading dose of 20 mg/kg divided into two equal doses administered intravenously 12 hours apart and a maintenance dose of 2·5 mg/kg every 12 hours. We obtained blood concentrations of phenobarbitone before the first maintenance dose and then at 3–5 days of age and adjusted the dose to achieve phenobarbitone trough blood concentrations of 20–30 μg/ml.

We obtained ultrasound brain scans on days 1, 3, and 7 of life and subsequently at weekly intervals in infants with IVH. Haemorrhages were graded as follows: grade 1, germinal matrix haemorrhage; grade 2, intraventricular haemorrhage with normal ventricle size; grade 3, intraventricular haemorrhage with ventricular dilatation; grade 4, intraparenchymal haemorrhage. The data were analysed by Student's t test to compare the means and χ^2 test to compare the proportions in the two groups. Differences were considered significant if the value of p was 0·05 or less.

Results

The number of infants in the two groups who required assisted ventilation, treatment with bicarbonate, volume expansion, and indomethacin for patent ductus arteriosus was comparable. In addition, the number of infants who developed hypoxia (arterial oxygen tension <40 mm Hg), hypercarbia (arterial carbon dioxide tension >60 mm Hg), or pneumothorax was also similar. Blood concentrations of phenobarbitone (mean (SD)) before the

Table *Effectiveness of treatment with phenobarbitone in 30 infants compared with 28 control infants in reducing intraventricular haemorrhage (IVH). Values are number (%) of infants*

	No IVH	*Degree of haemorrhage*				*Total IVH*	*Deaths*
		Grade 1	*Grade 2*	*Grade 3*	*Grade 4*		
Treated infants (n=30)	13 (43)	1 (3)	2 (7)	9 (30)	5 (17)	17 (57)	4 (13)
Control infants (n=28)	9 (32)	3 (11)	6 (21)	8 (29)	2 (7)	19 (68)	4 (14)

Degree of haemorrhage: grade 1, germinal matrix haemorrhage; grade 2, intraventricular haemorrhage with normal ventricular size; grade 3, intraventricular haemorrhage with ventricular dilatation; grade 4, intraparenchymal haemorrhage.

first maintenance dose was 25 (9) μg/ml and after 3–5 days of treatment was 34 (19) μg/ml. No complications related to administration of phenobarbitone were noted except for apnoea in one infant who had a blood concentration of phenobarbitone of 65 μg/ml.

The Table shows the outcome of our study. Posthaemorrhagic hydrocephalus developed in four (14%) of the control group and in five (17%) of the group given phenobarbitone. There was no significant difference in the two groups with regard to the incidence and severity of IVH or mortality.

Discussion

Our results indicate that phenobarbitone administered in anticonvulsant doses to very low birthweight infants in the first week of life is ineffective in reducing the incidence or severity of IVH. These results are in contrast to those of Donn *et al*, who have shown a significant decrease in the incidence of IVH from 47% in control infants to 13% in treated infants. We achieved similar blood concentrations of phenobarbitone, which were maintained over the first week of life. We have also been unable to confirm the results of Bedard *et al* who have shown decreased severity of IVH in treated infants.[2] Our results are, however, in agreement with those of Morgan *et al* and Whitelaw *et al*, who were unable to show any benefit from treatment with phenobarbitone.[3 4]

In conclusion, despite achieving blood concentrations of phenobarbitone in our treated infants that seemed to be effective in one trial,[1] we were unable to show a decrease in either the incidence or severity of IVH in very low birthweight infants treated with phenobarbitone.

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Contemporary history

Child health in Nigeria: past, present, and future*

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I looked at the list of former Windermere lecturers and realised the great honour conferred on me by being invited to give this lecture. It is also a tribute to the vigour of Nigerian paediatrics and paediatricians, whose frustrations and achievements form the major part of this lecture, and to those paediatricians, mostly your members, who set us on our path—Dick Jelliffe, the late Bob Collis, Arthur Tompkins, Ralph Hendrickse, David Morley, Hugh Jolly, the late Bruno Ganz, the late Richard Dobbs, and Bob Prosser, to name a few—and to those of you in this country who have inspired, taught, and supported us in our gigantic struggle to improve the health of our children.

Before the arrival of paediatrics in Nigeria in 1952, children were given scant attention. The earliest health services were provided for sailors and slaves. Malaria took a heavy toll of the lives of explorers and missionaries who ventured inland, but the latter were the most persistent and dedicated to providing services for the indigenes. The government services were developed mainly to care for European civil servants and army personnel and were also preoccupied with eradicating malaria and improving sanitation. From 1900 onwards small hospitals and dispensaries were in evidence in towns with no medical missionary establishments. By 1925 Lord Lugard wrote:

> 'The diseases of tropical Africa are comparatively few; blackwater fever, malaria, dysentry and anaemia are the principal ones. Lung diseases, enteritis and cholera are rare or uncommon among Europeans. We have now, in the African Tropics, a most efficient medical service, and generally speaking, excellent hospitals with an adequate nursing staff. To the skill of the doctors and the improvements they have effected in sanitation etc, it is due that the returns of deaths and invalidings now show such a wonderful decrease.'[1]

The historian of the Nigerian health services, Ralph Schram, comments: 'Lugard undoubtedly felt that the advances were wonderful, but for 9·5 million Africans in Nigeria, the day of excellent hospitals and improvements in sanitation were still far off.'[1]

Dr I L Oluwole began the first school health services in Lagos in 1925, and maternal and child welfare services were established in the rural areas, mostly by missionaries, around 1926. One of the earliest was in Ilesha, where, many years later, Professor David Morley carried out his historic studies. In the 1920s it was noted that deliveries often took place on the mud floor. The rooms were dark, smokey, and overcrowded. The deliveries were supervised largely by grandmothers, who often introduced puerperal sepsis. The babies were left unattended until the third stage of labour, with oozing cords open to infection from tetanus, a risk only increased by dressing the cord with cow dung.

In 1930 consciences were stirred in Britain about the health of mothers and children in Nigeria, and Dr Mary Blacklock was sent out by the Leverhulme Research Foundation to investigate 'certain aspects of the welfare of women and children in the colonies', but little action was taken. In 1931 a report on health in colonial Africa stated that 'the main factors which led to high infant and general mortalities are lack of sanitation, widespread incidence of debilitating diseases such as malaria, helminth infections, schistosomiasis, and venereal diseases, lack of medical care, and dietetic deficiencies'. It is still so today, with a few more additions to the list.

Collecting of vital statistics became compulsory in Lagos in 1863. More than a century later, however, important statistical data were rare, and the little information that existed was not properly used. For example, in 1952, Dr S L Adesuyi, a medical statistician, stressed the stupidity of providing hospital beds almost exclusively for adults (90%) when children needed 40–50%. Moreover, the provision of beds for women was only 20% when about half of the patients were women.

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†Since giving this lecture Professor Ransome-Kuti has been appointed Minister for Health in Nigeria.

Infant mortality for Lagos was stated to be 450 per 1000 in 1900.[1] Fifty years later it fell to 86 per 1000 and in 1973 it was reported at 70 per 1000 and 44·7 per 1000 by the United Nations *Demographic Year Book* and the Federal Office of Statistics (Lagos), respectively. Because of the tremendous growth of the medical services and the prosperity of the people there has been a steady decline in infant mortality in Lagos and perhaps throughout the Federation; however, the method of reporting and collecting data is such that the vital statistics for the nation are still unreliable.

More reliable data are available from surveys. The Rural Demographic Sample surveys carried out in 1965–6 give the country's infant mortality as 178 per 1000, that of Lagos as 143 per 1000, and that of the former Western region and the former Federal Territory as 79 per 1000. The surveys also reported a child mortality (0–5 years) of 322 for boys and 306 for girls in rural Nigeria. Using age specific mortality, 40% of 1000 children born at year 0 will have died by the age of 5, most of these deaths occurring in the first year. Data from our paediatric emergency room at Lagos University Teaching Hospital also indicated that infants (0–1 year) have the highest mortality among children admitted.

With the opening of the first medical school in Ibadan in 1948, paediatrics arrived in the country in the early 1950s. Health problems began to be defined mainly as they presented in hospitals, and solutions were found where it was possible. There were, however, few community studies.

At that time, the ratio of doctors to population was stated as 1:40 000. The desirable ratio for a country in the African region according to the World Health Organisation was 1:10 000. Nigeria was determined to achieve that ratio as soon as possible in the hope that health care would thus be available to all. It did so in 1980, by which time 13 medical schools were functioning. The health of our children, however, has hardly improved.

Neonates

The high perinatal mortality attests to the poor quality of our obstetric care—45·6 per 1000 in Lagos,[2] 60·7 per 1000 in Ibadan,[3] and 52·3 per 1000 in Ife.[4] These hospital data (except the data for Lagos, which are for the whole city) include the outcome of deliveries attended in the early stages by traditional midwives and brought to hospital when they go wrong. In Lagos 38% of deliveries were assisted by traditional healers, or took place at home.

In 1981, in the rural areas of Bendel State, Akenzua found eight traditional midwives per 1000 population.[5] Among other responses he received from these midwives, 56% did not think it was necessary to wash their hands and 36% the perineum before delivery, and 20% would manage cases such as transverse lie and prolapsed cord and 92% breech deliveries on their own. They are often known to fail. Asked about the methods used to resuscitate a baby who fails to cry at birth, the answers varied from 'sprinkle alligator pepper on baby' (60%), to 'plug the anus with finger and pour cold water on baby' (8%), and 'Nothing! It's God's wish' (4%). All of them were willing, however, to be trained in modern ways of midwifery and practice to improve the quality of their service, and they are therefore a potential source of health manpower in the rural areas.

In a provincial hospital in Ondo with no paediatric unit, intrapartum asphyxia due to prolonged labour was the commonest cause of the high perinatal mortality. Other causes were prematurity, twinning (16·4%), and congenital malformations. In the University College Hospital, Ibadan, the causes of high perinatal mortality were twinning (10% of all pregnancies and also an important cause of prematurity), malpresentation, toxaemia, and the tendency of women in Ibadan to have large families.[3] The women admitted to the hospital in Obadan were highly selective, and that hospital also had an excellent paediatric unit.

Eighty per cent of babies are delivered in an unhealthy environment by unskilled attendants. In hospitals or health centres they are discharged into the same contaminated environment within 48 hours. Ill babies pour from the community into hospital wards where facilities are most inadequate. In Lagos in 1981, 35% of newborn babies admitted from the community were infected, 31·5% were preterm, and 19·5% jaundiced. Moreover, 1021 jaundiced babies were treated as outpatients, 677 of whom received exchange transfusions. Similar experiences have been reported from Ibadan and other centres.

Five conditions account for 76% of neonatal deaths in hospital—jaundice, infection, congenital malformations, tetanus, and low birth weight (ranging from 21·3% in the North[6] to 7·3% in Lagos,[7] for babies born in hospital). Infections, including tetanus, are the major causes of death. Except for congenital malformations, all the conditions stem from factors in the environment.

Neonatal jaundice is more severe in babies admitted from the community than in those born in the hospital, and glucose-6-phosphate dehydrogenase deficiency is the commonest cause among the former group. In 1967–8, 52% of children registered in our neurological clinic had cerebral palsy due to neonatal jaundice. In Lagos mothers of babies admitted for jaundice stated that they had used mentholated dusting powder on the umbilical cord. A controlled trial in infants deficient in glucose-6-phosphate dehydrogenase who had been born in hospital indicated that those who had had the powder applied to the umbilical cord developed jaundice more often and more severely.[8]

In 1983 it was reported that herbalists were familiar with jaundice in the newborn and believed it to be transferred from the mother (and occasionally from the father) to the fetus or caused by shortage of blood in the newborn, fever, mosquito bites, blood spilling into the eyes of the baby at birth, bad water in the baby's body, and the mother eating bananas during pregnancy.[9] They would treat it by administering concoctions of herbal medicine or washing the baby with black soap.

Older children

The emergency room, where only very ill children are admitted, is the busiest unit in academic paediatric departments. It is the point of entry from the community into the outpatient department and for 80% of admissions into the wards. It mirrors the health problems in the community and provides an indication that the community health support systems have failed.

Most conditions seen in the emergency room are preventable or easily cured if diagnosed and treated early. But these diseases are not 'interesting' to the 'tertiary' trained and situated physician until they occur in their worst form. The worst hit are children aged 2 years and below. These children constituted 94% of all admissions to the emergency room in Ibadan in 1968 and a similar proportion of deaths in Lagos. The situation remains the same in 1984.

Gastroenteritis and malnutrition

Nigeria is suffering the decline in breast feeding reported from various parts of the world. In Lagos in 1968 dietary histories of patients with malnutrition indicated that bottle feeding was added to breast feeding by all mothers during the babies' first month of life.[10] In Ibadan in 1973 a report to the United Kingdom Committee of the Freedom from Hunger Campaign showed that bottle feeding was started at less than 1 month of age by 52% of mothers, and 94% introduced bottle feeding by the age 2–3 months. In Lagos most mothers of malnourished children surveyed bottle fed their babies because they 'took a fancy' to it. In Ibadan mothers said that it gave the baby 'health and strength', concepts popular in Nigerian culture and often used in food advertising.[11]

Many mothers also stated that breast milk was not sufficient. Early bottle feeding is known, however, to lead to a possible failure to empty the breast, resulting in a dampening of the 'let down' reflex and reduced breast milk output. The need for bottle feeding is thereby increased and ultimately supervenes. When, because of ignorance or poverty, dilute formula feeds are thereafter given to the baby, marasmus develops.

Added to bottle feeding, the highly contaminated environment, poor personal hygiene, ignorance, and the dearth of a potable water supply also account for the high incidence of gastroenteritis.

Oral rehydration therapy is gaining ground rapidly and saving many lives. Its use was taught to mothers in our primary health care service in Lagos. After fours years a community survey indicated that 61% of 247 registered mothers knew the correct formula but only 32% of these had used the solution during their child's last episode of diarrhoea, which showed a reluctance of mothers to take responsibility for the care of a condition which, in their experience, could lead to death. At the same time, the dread of a depressed fontanelle is clearly shown by potions and pastes applied to it, but which is not associated with loss of fluid and the need to replace it. More efforts are needed at community level to promote the use of oral rehydration solution by mothers.

Most children are weaned on maize gruel. This inappropriate feeding practice at the weaning period, whereby culture or ignorance dictates that predominantly carbohydrate diets are fed to the infant, is a major cause of diarrhoea and malnutrition. This is in spite of the fact that there are staple food items in the community suitable for weaning infants successfully.

In Ilesha the mothers of malnourished children knew of the disease protein energy malnutrition, 64% calling it 'kosoko' (no hope) or 'orinla' (big head).[12] They believed that the child had 'supernatural powers' to die and be reborn. They also believed that the disease was communicable. None mentioned an inadequate diet as the cause.[12]

Children with malnutrition seen in hospital are the tip of the iceberg, with a large reservoir of potential cases ready to be struck down by measles, tuberculosis, whooping cough, and diarrhoea. It is necessary, therefore, to restore the mother's confidence in breast feeding and instil into her relevant and effective weaning practices, otherwise our present knowledge about infant feeding will have been acquired in vain.

Malaria/convulsions

In the clinics malaria presents as fever. It is the commonest complaint, most frequent and severe in children aged between 9 and 24 months. By age 5 years the clinical manifestations of malaria are less severe, and the child has acquired considerable immunity. It is therefore rare for malaria to be the cause of death in this holoendemic area in older and school children, but the infection does give rise to a high prevalence of morbidity.[13]

This pattern, however, is changing due to the widespread use of antimalarial drugs. For example, in the rural clinic established by David Morley in Imesi-Ile, where the children were given pyrimethamine prophylaxis, parasite rates were lower in patients in the treated than in the untreated village.[14]

The most severe forms of malaria are seen in hospitals. One form presents with high fever and prolonged convulsions. It is also common in children aged between 9 months and 3 years. Thirty to 40% of the children die within 72 hours of admission. Malaria parasites can be shown in the blood film of a third of the patients. The disease is dreaded by the parents, who believe that when the children clench their teeth death is imminent. To prevent this disaster, the child's mouth is severely traumatised in the attempt to keep it open. In one case, a father squeezed the buccal pad of fat into the child's mouth by exerting pressure on both sides of the cheek. Shock treatment is also applied, such as burning of the feet or buttocks or rubbing pepper into the eyes.

A mixture containing mainly cow's urine, tobacco leaves, and various herbs, shown to cause hypoglycaemia in rabbits,[15] is given to many. This poison is a major contributor in about 60% of the deaths due to this condition.

We surveyed mothers in the community regarding the use of cow's urine mixture; 27% gave it to their children regularly once, twice, or more daily, on its own or mixed with herbs or other medicines, and, in most cases, the child always improved. The mixture is given routinely to prevent convulsion, and so when the child convulses, a large amount is poured down his throat. This is the community's perception of a drug now known to be poisonous. Its use is considerably reduced in the urban areas but continues in the villages.

An ideal regimen for malaria would be one by which the child could be partially protected so that he did not develop a severe attack of malaria and at the same time would still be capable of manufacturing antibodies against the parasite. One such regimen was described by Morley in 1971 in which pyrimethamine was given monthly and chloroquine administered for any episode of fever.[16] With this regimen, the number of febrile convulsions in the children in the community was considerably reduced, presumably due to the prevention of those caused by malaria. At the same time, the children were given an opportunity of developing immunity to malaria.

Measles

Of all the infectious diseases amenable to prevention through immunisation, measles is the most devastating. A high level of coverage with its vaccine is difficult to achieve because of expense and fragility. Although measles immunisation is recommended at the age of 9 months, in Lagos, for example, it is estimated that 30% or more of measles cases occur before that age, and vaccination at 6 months has often been ineffective. The fact that the child develops measles after immunisation erodes the mother's confidence in the vaccine and brings it into disrepute. In the Cameroons, workers from the Center for Diseases Control, Atlanta, Georgia, have documented a drop in the incidence of measles in the 0–8 months age group from 88·2 per 1000 to 31·8 per 1000, with a vaccination coverage of 40% in 9 month old infants.[17] They also expect that higher rates of coverage in the 9–23 year age group will further reduce its incidence in the under 9 month age group.

From the evidence available in Nigeria, the performance of our Expanded Immunisation Programme since 1976 has been dismal. Evaluation in the Oranmiyan Local Government Area of Oyo State found very low levels of immunisation coverage for diphtheria, pertussis, and tetanus, polio vaccine, and measles vaccine between 1977 and 1981.[18] The reasons for the poor performance were identified as:

(a) inadequate community participation in the planning and implementation of the programme;
(b) poor communication between different government representatives; and
(c) inadequate publicity.

Moreover, vehicles were grounded for most of the year and frequent power failure caused wastage of large quantities of vaccines, which cast doubt on the potency of those administered to the children.

In 1984 it was reported that no child in Tafawa Balewa Local Government Area, Bauchi State, and only 9% in Owo Local Government Area, Ondo State, were fully vaccinated after three years of the programme. Irregularities in financing of the State and Federal Health Ministries led to erratic purchase and distribution of vaccines. A lack of planning to involve the grassroot implementers and inadequate training and poor supervision were also found. None of the refrigerators at the local government office and the two health clinics visited were functioning because of power failure, nor was the stand by generator working. Considerable amounts of vaccines were spoilt due to neglect in monitoring vaccine storage temperature and potency. More than 94% of mothers did not know why their children were being immunised and at what age they should be immunised.

In spite of these gross deficiencies, the implementation of this programme was revised in Owo with the aid of UNICEF in 1983 and has resulted in a 38% coverage of children aged 1–2 years with target immunisation in the first month of the reactivated programme and 58% by the fourth, indicating that with commitment, efficient organisation, and management the immunisation state of our children can be considerably improved.

Running through this discussion is a well known theme—that children in developing countries are so ill and die in such large numbers because of the inimical environment in which they live. The human, socioeconomic, cultural, and environmental elements of the society, therefore, need to be transformed. Most of our people still believe in and utilise traditional medicine born out of superstition, spiritualism, and the worship of ancestors ingrained in us during our evolution over centuries. Many of us who have acquired the skills of modern scientific medicine were catapulted from a traditional past to this new era, perhaps in a generation. Just as when a pagan becomes a Christian, we tend to turn our backs on the past, enshrined in the community, and look to the future—the life and medicine of the developed world—forgetting that even that had a traditional past and developed through a process of research and application of its results. We have to go back to where our people are and evolve with them.

Most of our doctors, and particularly paediatricians, work in the pinnacle of the health care delivery system—the teaching hospitals—perpetually reaping the morbid harvest of the contaminated community. We do not possess the skills to work with and transform the community to stem the tide of ill children.

Asuquo Antia, one of our distinguished paediatricians, once sounded 'a note of caution to all those concerned with child health in the Tropics that all change is not progress and that increased sophistication does not necessarily mean advancement.'[19] But the question to be asked is, 'What change do we need to ensure progress?'

David Morley in the early 1950s worked in Nigeria and was the first to see the need for innovations in the delivery of child health services. Because of the shortage of doctors at that time he transferred most of the responsibilities for treating the early stages of the common diseases to nurses. Since then, we have learned that even lesser trained health personnel, down to the level of the village health worker, can be successfully trained to assume some of these responsibilities.

Morley integrated preventive and curative services; introduced the home based record system; the 'road to health' chart; simple diagnostic tools such as the arm circumference strips; and therapeutic skills such as the use of salt, sugar, and water solution to prevent dehydration. Although he showed a reduction in mortality and morbidity in the treated villages using limited resources, the system rapidly deteriorated after his departure because there was no government and community participation.[14] Of the two, the latter is the key to effective health services. Community participation means that the citizens control the process of transformation whereby they mobilise and act to improve the quality of their lives. In this process existing social structures or those created for the purpose, such as village health or development committees, must be the medium. Appropriate health technology must, as much as possible, be transferred to and used by the members of the community. On the other hand, local technologies found to be effective should be encouraged—for example, the Hausa cut the umbilical cord with a red hot knife. For this reason, tetanus is relatively uncommon in their newborns. At all times the aim is to develop the spirit of self reliance within the community and incorporate patterns of scientific health care into the traditional system. Properly motivated, the community will take action in its own interests towards achieving better health.

Mothers are our best ally in this enterprise. It is the uneducated woman (and they are in the vast majority) who bears the largest number of children and loses the most, who fails to understand simple concepts such as the meaning of the growth chart, and who performs worst of all in bringing her child for immunisation even when the services are made available, affordable, and accessible and are efficiently run. She is subjected to enormous social and cultural constraints that prevent her from utilising the services effectively and is also subjected to conflicting advice from ancient and modern health systems regarding the care of her child. In any case, the father's role in these health decisions is often dominant. Moreover, the mother is striving to function in a modern economy with inadequate, inappropriate, or no educational preparation.

It is difficult to convince mothers of the need and efficacy of preventive measures, hence elaborate 'outreach' or community based systems must be set up to induce her to use the services. For example, an infant's first visit to a health facility is usually for an episode of illness, often occurring past the age of 6 months when the first phase of immunisation should have been completed, and at a time when the child is most vulnerable to preventable infectious diseases.

There is evidence indicating that when adequate spacing or a reduced number of children per family is achieved their health improves. For example, as the size of the family increases so the chances of malnutrition,[20] low birthweight babies, gastroenteritis, respiratory infections, and a lowering of intelligence quotients also increase. Arguably, if parents perceive that their children will survive due to efficient child care services they will take steps to reduce the size of their families. Evidence in support of this hypothesis comes from Imesi-Ile, where it was found that the desire for additional births was less in the village with an efficient clinic for the under 5s than in one without.[21]

In Ebenbo village in Cross River State it was concluded that the women compensate by having additional children almost exactly equal in number to the number of deaths they have had, and that if child mortality can be reduced, there might well be a corresponding decline in completed family size.[22] The smallest families are those of the highest social class, and they also have the lowest infant and child mortality.

The challenge is to establish a health care system that will touch the lives of every member of the community, especially children, who are the most vulnerable, and that will tackle those conditions causing the highest mortality and morbidity. The system must be organised from the grassroots, integrating preventive, promotive, and curative services; using the type of technology that the members of the community will accept, at a level they can utilise, maintain, and afford, and with an efficient and effective system of supervision and referral.

A first step is to study the principles underlying the implementation of such a system in a traditional setting. Without this we cannot reasonably expect to supplant a traditional health system that the people have learnt to trust, that is serving them well, and whose language is understood and verdict accepted. Traditional medicine demands compliance through dogma, communal pressure, and faith; scientific medicine demands reasons and proof, attributes acquired through modern education.

National programmes require political will and social and economic reforms. But, while waiting for these, the health technology should be put in place. This should be the function of the universities at this time. Of all the tasks (preventive, promotive, and curative) necessary to improve the health of the population, only curative ones are predominantly emphasised and taught in medical schools.

Doctors are acknowledged leaders in the health care systems, and their opinions are sought and respected by governments. To be effective as an advocate for relevant services of the kind described above, our doctors should be trained to head a primary health care system and also to function as a house officer in a hospital on qualification. To accomplish this type of training, our medical schools should have a model primary health care practice area in which to teach community care to a standard of excellence, just as a teaching hospital is required to teach individual care. Fortunately, this need is being recognised and accepted, and medical curricula are being revised to train doctors with the relevant knowledge, attitude, and skills to tackle our health problems in our own setting.

The slogan is 'Health for all by the year 2000'. There never has been health for all, and never will be, but we can make health care available and accessible to all by the year 2000.

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Personal practice

Medical evidence in child abuse

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In the light of recent fatalities and other unfortunate episodes where proper attention to medical evidence might have averted disaster, it is a timely moment to evaluate the sort of evidence paediatricians should present in child abuse cases and how to do so in such a way that it cannot be ignored, overlooked, or discounted. To make a maximum impact at case conferences and in court, it is essential that paediatricians are clear about three major issues:

(1) The nature of medical evidence in child abuse;
(2) The rules governing evidence presented in care proceedings;
(3) The central role of the paediatrician in representing the interest of the child above all else.

Child abuse is defined as the avoidable impairment of any aspect of development as well as physical well being. The areas in which the paediatrician has special expertise include physical injury; nutritional status; growth; and intellectual and psychological development. This expertise lies outside the sphere of social workers but is supplemented by the opinions of child psychiatrists, psychologists, and speech therapists. It is the paediatrician, however, who has the general responsibility for collating this evidence, which should have authority that can be challenged only by another expert, that is, another paediatrician. Thus, any abused child who comes under the care of a paediatrician should be assessed in all the areas listed so that the medical evidence can be built up. The complete picture, that is evidence of deficiencies in more than one of the parameters, is far more important than any one feature. While it is not possible, for example, to say that a child with speech delay must be neglected, if the speech delay is associated with physical injury or unexplained growth failure, it is reasonable to conclude that it is 'likely' that home circumstances are responsible for both deficiencies. The more deficiencies there are, the more likely the conclusion. The witness should not be deterred from maintaining such an opinion even if it is put to him or her that the finding could have some other explanation. Any doubts should be resolved in favour of ensuring that further abuse is prevented.

It is clear from previous studies that children living in abusing homes have, at best, an uncertain outlook, irrespective of the support offered to families,[1] [2] with a considerable risk of death, serious illness or injury, education failure, emotional disturbance, and the likelihood of being taken into care in later childhood because of delinquency. Fear that medical evidence will lead to the break up of a family is not justified by the poor outlook for these families.

Growth failure is an important feature of child abuse.[3] [4] Continued poor growth is associated with poor intellectual performance.[5] [6] We have found that children who have failed to grow adequately in abusing families show poorer catch up growth if allowed to remain in those families[7] and that this poor growth is associated with evidence of more than one feature of child abuse. There is, therefore, a prima facie case for removal of these children into foster homes.

This case has been seriously weakened in the past by confusion over the outcome for children in care. They were often removed from their own parents late in childhood or subjected to repeated changes in rearing with the child being switched among children's homes, natural parents, and foster homes. The problem has been recently compounded by the influence of the 'parents' rights' lobby who have, by various means, made it increasingly difficult for children to be placed in long term care with a view to adoption. Little wonder that some have been led to conclude that natural homes are preferable to that. Yet early removal to permanent foster homes tells a very different story. At all events, paediatricians should not be tempted to 'soft pedal' their evidence or views because of such considerations.

Since the only objective evidence that the child is being abused comes from the medical evidence, it should be central to any decision making. It will, however, only be so if the witness is clear of the strength of the case and understands how to present the information to the court. It is evident that for those children with more than one feature of abuse, the long term outlook is relatively poor, particularly when one of the features is growth failure and especially when catch up growth can be shown in hospital or in a foster home. In these cases, the paediatrician is entitled to conclude that on balance speech delay, or poor growth, or behaviour disturbance is due to inadequate rearing and that the long term consequences for the child if it continues to be reared in the same way are likely to be unfortunate.

This brings us to the crucial question of the nature of the evidence presented in court. In the first instance, the rules of evidence are those of the civil law. The paediatrician does not have to show beyond reasonable doubt that speech delay is due to neglect (a virtually impossible task) but merely on the balance of probability that this is so. Thus, a child who has failed to grow and shows speech delay in the absence of other causes can be said to be having its development avoidably impaired.

It is also important to recognise that some of the medical evidence is material, that is that the child has failed to grow, or is not talking, or has bruises etc; but that some of it is expert, that is the interpretation of the bruises, the relation between poor speech and growth failure, and the likely long term consequences if this is allowed to continue. It is vital that the consultant paediatrician should appear as a witness in cases of such complexity, and not a junior member of the consultant's staff. Only a person of some seniority can have the authority to express opinions of this kind directly to the judge or magistrate over the heads of solicitors or council. It is important to know that this is possible and that one is not restricted merely to answering questions during cross examination.

The paediatrician has two tasks, to present the evidence of abuse and then to express an opinion as to what would be required to prevent that abuse recurring. In cases where more than one form of abuse is evident, it is perfectly proper to state that medical evidence shows that on balance of probability home circumstances, whatever they are, are unsuitable for child rearing and that unless they can be substantially altered it would be unwise for the child to return home. This avoids the risk of being accused of hearsay evidence. If challenged, the response would be that poor home circumstances could be inferred from the condition of the child and was not based on hearsay. It can also be said with some confidence that current policy for the early return of seriously abused children under care or supervision orders while case work is carried out seems to have little basis in terms of results to support it, and this can be stated as an opinion if asked whether a case order or supervision order should be made. At the very least, paediatricians should insist on regular follow up for anthropometry, developmental testing, and speech delay, with appropriate action if the findings warrant them.

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Correspondence to Dr L S Taitz, The Children's Hospital, Sheffield S10 2TH.

Archives of Disease in Childhood, 1986, **61,** 207–208

Correspondence

Immunoprophylaxis of infants born to hepatitis B virus exposed mothers

Sir,

We hope that the paper by Ewing and Davidson[1] on a fatal and fulminant hepatitis B virus infection in a 10 week baby born to white parents, with hepatitis B surface antigen (HBsAg) negative father and HBsAg positive, hepatitis Be antigen (HBeAg) negative, HBe antibody positive mother, should nullify the concept that HBe antibody positivity in a pregnant mother reduces the apparent risk of perinatal hepatitis B virus transmission. Apart from the present case, there have been at least three similar instances of hepatitis B virus infection in babies of anti-HBe positive mothers.[1] The mother, in the present case, should have better been tested for hepatitis B virus DNA because this has emerged as a more reliable index of viral replication than HBeAg, DNA polymerase activity, or aminotransferase activity.[2] The baby blood, like the maternal sample,[1] should have been tested, for the satisfaction of purists, for IgM antibody to hepatitis B virus core antigen.

Immunoprophylaxis of infants should not only be confined to offsprings of HBsAg positive mothers but extended to infants born to those who are in the 'window phase' with antibody to core antigen but without HBsAg and antibody to HBsAg. That alone can ensure that fatal and fulminant episodes of hepatitis B virus in the infants born to any low level carriers[3] among those in 'window phase' should stand prevented. Studies with high affinity monoclonal antibody for HBsAg[4] should categorise such pregnant women along with HBsAg/HBeAg/hepatitis B virus DNA positive females as potential dangers for perinatal hepatitis B virus transmission.

S C ARYA, S J ASHRAF, AND C M PARANDE
King Fahad Central Hospital and
Gizan General Hospital,
Gizan,
Saudia Arabia

Drs Ewing and Davidson comment:

It is well recognised that there is a high risk of transmission of hepatitis B virus to the infant at birth when the mother is both HBsAg and HBeAg positive, while babies born to HBsAg carrier mothers who have detectable HBe antibody are at low risk of acquiring hepatitis B virus infection. Thus it was reported[5] from two West London hospitals that nine of 10 (90%) infants born to HBeAg positive mothers acquired HBsAg compared with three of 38 (8%) of those born to HBe antibody positive mothers. We cannot agree, therefore, with Arya *et al* that the concept that HBe positivity reduces the risk of perinatal transmission should be nullified. We agree, however, that there is a case for giving immunoprophylaxis, including passive immunisation with hepatitis B immunoglobulin and active immunisation with hepatitis B vaccine, to all babies whose mothers are HBsAg positive, irrespective of their HBeAg or HBeAb state. It must be noted, however, that supplies of hepatitis B immunoglobulin are limited[6] and *for that reason* it may be necessary to give priority to infants of HBeAg positive mothers.

We accept that of the current tests for hepatitis B infection, that for hepatitis B virus DNA is probably the most reliable index of viral replication. When this child was investigated, however, tests for hepatitis B virus DNA were not available to us and are still not used routinely in most centres. Since our report was published a stored sample of serum from the mother has been examined by Professor A J Zuckerman and Dr T J Harrison at the London School of Hygiene and Tropical Medicine, who have reported that hepatitis B virus DNA is present but just at the limit of detectability.

Arya *et al* suggest that the infants blood should have been tested for IgM antibody to hepatitis B virus core antigen, 'for the satisfaction of purists'. We cannot understand this comment because such a test would be used to determine whether HBsAg detected in the blood was the result of recent infection or long term carriage and would clearly not be relevant in a 2 month old infant. Moreover, Chen *et al*[7] were not able to detect IgM core antibody until 9 months of age in any of 86 infants, 31 of whom developed HBsAg, born to HBsAg carrier mothers.

Arya *et al* refer to the theoretical possibility that HBsAg negative, core antibody positive mothers may transmit hepatitis B virus infection to their offspring. We are not aware of any evidence that this happens in practice and until there is such evidence we cannot agree that immunoprophylaxis is necessary for these infants.

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Measurement of urinary constituents and output using disposable napkins

Sir,

Drs Roberts and Lucas[1] have produced an excellent and carefully conducted study that should give more confidence to those performing metabolic studies on babies. I would issue a note of caution, however, to any considering using this method in the premature newborn.

Low birthweight neonates often have irregular, infrequent, and incomplete bladder emptying and may pass only 0·5 or 1 ml at a time. Urine volume measurements based on weighing cotton wool balls or even nappies will be imprecise, more so because in our experience there is considerable evaporation, even inside an enclosed, humidified incubator. Furthermore, for the same reason, the urine samples from successive micturitions cannot be pooled, so that measurement of excretion of urine constituents over a period long enough to avoid inaccuracy due to incomplete bladder emptying will depend on multiple estimations on several samples, making the procedure cumbersome.

B H Wilkins
Southmead Hospital,
Bristol,
England

Drs Roberts and Lucas comment:

Dr Wilkins is mistaken in his suggestion that our new method for measuring urine output in infants[1] is not suitable for use in low birthweight infants. The problems he describes, infrequent and incomplete bladder emptying, apply equally to the traditional method of using a urine bag and, in any case, are irrelevant to methodological precision as the method is designed to measure urine output not urine synthesis. A separate consideration is the precision of the balance used to weigh the napkins—it should, of course, be related to the amount of urine being measured (a sample of 0·5–1·0 g requires a precision of at least ±0·01 g). Dr Wilkins also suggests that error may be incurred by the urine evaporating from the napkins. Part of our study, however, was designed to measure the rate of evaporation, and the value obtained was reported (less than 0·4% per hour in a close fitting napkin). We suggest that any problem he has experienced with evaporation may well be due to a lack of care in positioning the napkins. His final point, that the method is cumbersome, is also incorrect; weighing napkins and pooling samples for laboratory analysis are extremely simple procedures compared with trying to keep a urine bag on an infant (boy or girl).

Reference

[1] Roberts SB, Lucas A. Measurement of urinary constituents and output using disposable napkins. *Arch Dis Child* 1985;**60**:1021–4.

. . . And children first?

Sir,

I am the convenor of the British Paediatric Association/British Association of Paediatric Surgeons Accident Committee. I can assure Dr Choonara[1] that we are working actively both as a committee and in close association with the Child Accident Prevention Trust (CAPT) to save children's lives and to improve the quality of their lives by reducing accidents to children.

The CAPT has set up a working party of which I am a member to look at what can be done to improve the safety of children in cars and to make recommendations about how these can best be implemented.

Examples of topics with which the Accident Committee is currently involved are to press for the safer packaging of drugs to reduce the dangers to young children and to discuss with the toy manufacturers the possibility of making small plastic toys radio-opaque so that in the event of their being inhaled or swallowed they are easier to identify and remove. There are many others.

The previous convenor of the Accident Committee, Dr Hugh Jackson, is the medical advisor of the CAPT and has been responsible for many valuable papers and seminars about hazards to children and has done a great deal to promote interest and involvement of other professionals—for example, architects, town planners, etc.

We would like more paediatricians to be interested in this subject.

Reference

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C Illingworth
Sheffield,
England

Injections and Asian children

Sir,

Asian children, particularly between the ages of 1 and 5 years, tend to be more difficult to examine than an English child of similar age. In most Asian homes a child is often threatened with being taken to the doctor and given an injection if he does not behave.

In the outpatient situation those of us who understand the Asian language often hear mum say that 'he is not going to give you an injection'. At this the child, who may have been quite cooperative up to that point, bursts out crying and becomes difficult to examine at the very mention of the word 'injection'. This, I feel, is one of the reasons why many Asian parents fail to keep their child's appointment. To make our task and that of the general practitioner easier, community doctors and health visitors should positively discourage this habit of threatening the child at home.

A Rashid Gatrad
Birmingham University,
Birmingham,
England

Book reviews

Health Services in Schools—a New Look. By Kingsley Whitmore. Pp 143: £4·95 paperback. Spastic International Medical Publications/Blackwell Scientific Publicaions Ltd, 1985.

This book grew out of a series of papers prepared by Dr Whitmore for the execuive of the now defunct Association of Clinical Medical Officers ('Si monumentum equiris . . .'). After a brief historical inroduction it presents a comprehensive documentation of the work of the school health service and discusses the influence of social disadvantage, ethnic origin, and other relevant factors. A review of present organisation and methods then leads to a ritique of the service and to proposals for he reform of clinical strategies and of taffing and structure.

It would be difficult to overpraise this unpretentious book. The malaise of the chool health service has been debated, and deplored, by a profusion of wise physicians; but Whitmore's mastery of the many complex issues, his clarity of exposiion, and his robust common sense raise his monograph to the status of a minor classic. t has relevance both for individual profesionals, whether doctors or nurses, concerned to improve the quality of their own contribution, and for those in administraive or managerial capacities who have the authority and the will to regenerate the service as a whole. Many others, including eachers, GPs, and (perhaps especially) hospital based paediatricians, will read the book with equal profit and in the convicion, if this reviewer's experience is any guide, that Whitmore has established an rrefutable case for the full rehabilitation of he school health service. His argument is lluminated throughout by an insistence on he twin principles of genuine team work between all the relevant disciplines and of he recognition of the full professionalism and clinical autonomy of the school doctor and his or her nursing colleague, hopefully released from the administrative irrelevancies that have shackled them for so long.

Blemishes are few and trivial. The section on positive discrimination is somewhat glib and superficial, and that on professional cooperation flows less limpidly han the rest. Far more importantly, how opportune that this book should appear ust when health authorities are making crucial decisions about the organisation and thrust of their clinical services! If it commands the widespread attention that its low price, readability, and importance so richly deserve the outcome could well be that long awaited new sense of hope and purpose for our educational health services.

H MCC GILES

Current therapy in allergy, immunology and rheumatology 85–86. By Lichtenstein, Fauci. Pp 272: £44·00 hardback. Blackwell Scientific, 1985.

This multi-author book from North America is the second edition to update information on the treatment of the diseases in question. In this volume there are 72 chapters, and of these only five are directly related to paediatrics—that is, asthma, food sensitivity, insect sting allergy, autoimmune thrombocytopenic purpura, and juvenile rheumatoid arthritis. As in any multi-author book the quality of the contributions is uneven. Also more than adequate attention is paid to the clinical details of each diagnosis, thus curtailing the space for the therapeutic advice. In general, there are no rigid guidelines for treatment of the diseases discussed in this book. The chapters on immunology are excellent and explain the therapeutic approach to immunological disorders in detail. It is a pity that the chapter on juvenile rheumatoid arthritis does not give a detailed account of the non-steroidal, anti-inflammatory drugs being the first line antirheumatic drug therapy. There are noticeable gaps. For example, there is no mention of Kawasaki's disease, monoarthritis, and psoriatic arthritis.

All in all this book provides a useful source of reference for those clinicians especially interested in rheumatology, allergy, or immunology.

K M GOEL

Child Health—a Textbook for the D.C.H. Edited by D Harvey, I Kovar. Pp 374: £22·00 hardback. Churchill Livingstone, 1985.

This book is directed towards doctors preparing for the DCH examinations, and, in its 30 chapters by various authors, sets the child health scene and covers early child development, preventive care, and the identification and treatment of the more common childhood problems likely to be met in primary care. In addition, appropriate information is given about investigation, treatment, and management at secondary care level, to enable the primary care doctor to advise, counsel, and support the family as necessary. There is also a chapter on tropical child health, emphasising the fact that three in four of the world's children are thus distributed. Finally, there are useful chapters on emergency procedures, prescribing, and, returning to the primary aim of the book, advice relating to examination technique and helpful examples of multiple choice questions.

The book, therefore, while appealing mainly to DCH candidates, will also be useful to those doctors offering a comprehensive child health service at primary care level.

The chapter on accidents and child abuse is timely and informative. It provides the reader with the opportunity of sharing the understanding of this complex subject with its experienced author (Dr Cooper), who also gives a valuable update on adoption procedures. Reference to sexual abuse is concise and acknowledges its growing importance. A more detailed account of the practical aspects of the procedures used in development screening would be welcome. For example, references to the testing of hearing are brief, and an examination candidate will need to turn elsewhere for information about these aspects.

While applauding the emphasis given in the book to the desirability of moving prevention into general practice, little is made of the need to ensure total child population cover or the need to collect data on a similar population basis to plan and monitor services appropriately. The school health service is referred to briefly, but educational medicine as such is not clearly defined, and information about special schooling is inaccurate.

These points aside, however, the book is attractively set out and provides candidates with a useful base from which to prepare for the DCH examinations.

MARION MILES

Archives of Disease in Childhood, 1986, **61,** 210

British paediatrics

Training for paediatrics with a special interest in respiratory disease

The Joint Committee on Higher Medical Training (JCHMT) has recently issued its first training programme for paediatricians wishing to practise with a special interest in respiratory disease. This training programme is set out in the standard JCHMT format and begins with the general observation that trainees who intend to take a special interest in respiratory disease will have to obtain sufficient training in general paediatrics to become accredited and must also have a total of not less than two years' experience in respiratory disease.

General professional training should occupy the usual three years after full registration, within which the trainee should hold a resident post of at least six months' duration with duties largely in the care of the newborn. A six month appointment in a unit providing respiratory intensive care is also desirable during general professional training.

In the course of higher specialist training, which should cover a period of not less than four years, the trainee must obtain the obligatory experience detailed in the training programme for general paediatrics and should also acquire experience in those areas which are of importance in the management of respiratory disease. These include intensive care, respiratory function testing, respiratory allergies, and the community care of children with respiratory problems.

Within higher specialist training a continuous period of one year, or interrupted periods totalling one and a half years, should be devoted to the care of children with respiratory disease, under the supervision of a consultant with a major interest in the field. This special experience should include participation in related research, with the analysis and presentation of data, and some practice in the administration of respiratory services is desirable. In view of the many respiratory problems that arise in the management of neonates, up to 50% of the obligatory experience in paediatric respiratory disease may be obtained in a regional neonatal intensive care unit.

Experience that is recommended rather than obligatory includes immunology and infectious disease, adult chest disease, adult intensive care, and paediatric cardiology. Additional training and experience in basic science disciplines would also be acceptable to the JCHMT provided it was relevant to paediatric respiratory disease and was appropriately supervised.

In line with the current view that training programmes should be flexible the JCHMT recognises that some trainees may become accredited by a different route from the one outlined.

A D M Jackson

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Contemporary Issues in Fetal and Neonatal Medicine

Perinatal Anesthesia

Volume 1: Edited by J.W. Scanlon

1985. 352 pages, 22 illustrations. £32.50

This volume provides a discussion, along the biological continuum of perinatal medicine, of the interactions between anaesthetic agents and the many conditions of pregnancy or neonatal life which require anaesthesia or anaesthetic drugs. Recent significant advances in several areas and new controversies in others are discussed. The contributors are all active researchers in their field, and cover topics ranging from the theoretical to the practical. Recently advanced concepts are explored, such as behavioural teratology, the beta endorphins and obstetrical intravenous fluids as fetally active drugs, and previously reviewed topics, such as the impact of obstetrical anaesthesia on newborn neurobehaviour and anaesthesia for the newly born, are given new insights.

Contents: The toxicokinetics of anesthetics and analgesics during labor and delivery *A. R. Scialli & S. Fabro;* Psychoteratology: behavioral effects of drugs administered during pregnancy *A. R. Hollenbeck & R. Smith;* Anesthesia during pregnancy: interaction with maternal disease *W. D. R. Writer;* Anesthesia for surgery during pregnancy *R. W. Knapp;* Maternal obstetric medication and newborn behavior *Carol M. Sepkoski;* Regional anesthesia for labor and delivery *A. B. Freeman & G. W. Ostheimer;* Maternal-fetal fluid, electrolyte, and glucose homeostasis *L. Grylack;* Anesthesia for the neonate *A. A. Jeon;* Anesthesia for high-risk pregnancy *Diane R. Biehl;* Endorphins *Therese K. Abboud;* Anesthesia for diabetics, labor, and delivery *S. Datta.*

Perinatal Brain Damage

Volume 3: Edited by Karen Pape and J. Wigglesworth

In preparation. 250 pages, illustrated. About £30.00

The expert contributors to this volume provide a practical discussion of the causes and treatment of perinatal brain damage.

Contents: Current problems in brain pathology *J. Wigglesworth;* CT — the state of the art *C. Fitz;* Ultrasound — the state of the art *D. Martin;* Birth asphyxia — scientific studies *J. Hellmann;* Birth asphyxia — clinical problems *G. Goldstein;* Intraventricular hemorrhage *Janette Goddard-Finegold;* Cerebral blood flow management *P. Rolfe & Kathleen Costeloe;* Prevention and treatment of GLH/IVH *R. Cooke;* Diagnosis and management of hydrocephalus *H. Hoffman;* Follow-up of neonatal brain injured children *Karen Pape;* Plasticity of the pre-term brain *J. Wigglesworth.*

Retinopathy of Prematurity: Current Controversies

Volume 2: Edited by W.A. Silverman and J.T. Flynn

1986. 352 pages, 117 illustrations. About £32.50

In this collaborative volume, paediatricians and ophthalmologists present the state of current knowledge about the retinopathy that effects premature infants. Each of the contributing authors was encouraged to develop his or her arguments without regard for a need to establish a consensus, the intent being to highlight areas of disagreement and uncertainty. Thus, while there are many areas of overlap in the chapters, the interpretations of the same evidence are not necessarily congruent. Current debates about the contributory roles of supplemental oxygen, light, blood transfusions, hypoxemia, hypercapnea, and the confused status of new treatments (including surgical interventions), as well as the familiar prophylaxis with vitamin E are all covered in this thought-provoking volume.

Contents: Overview: a 'developmental' retinopathy reconsidered *W. A. Silverman & J. T. Flynn;* An international classification of retinopathy of prematurity *J. T. Flynn;* The pathology of retinopathy of prematurity *A. Garner;* Animal models of retinopathy of prematurity *G.A. Cole;* Perinatal retinal vascular physiology *R. W. Flower;* Initiating events in the development of retinopathy of prematurity *F. L. Kretzer & Helen M. Hittner;* Monitoring and controlling neonatal oxygen therapy *J. D. Horbar;* Vitamin E and retinopathy of prematurity *Dale L. Phelps;* Retinal ablative therapy for active proliferative retinopathy of prematurity *E. A. Palmer, A. W. Biglan & R. J. Hardy;* Retinal detachment in retinopathy of prematurity *W. Tasman;* The ocular sequelae of regressed retinopathy of prematurity *B. J. Kushner;* Epidemiology of retinopathy of prematurity *Eva D. Alberman;* Developmental issues in blind infants and children with retinopathy of prematurity *S. W. Teplin.*

Routines in Neonatal Care

Volume 4: Edited by R. Cooke

In preparation. 250 pages, illustrated. About £30.00

In this book a group of specialists provide a critical discussion of the routines employed in the management and treatment of the newborn.

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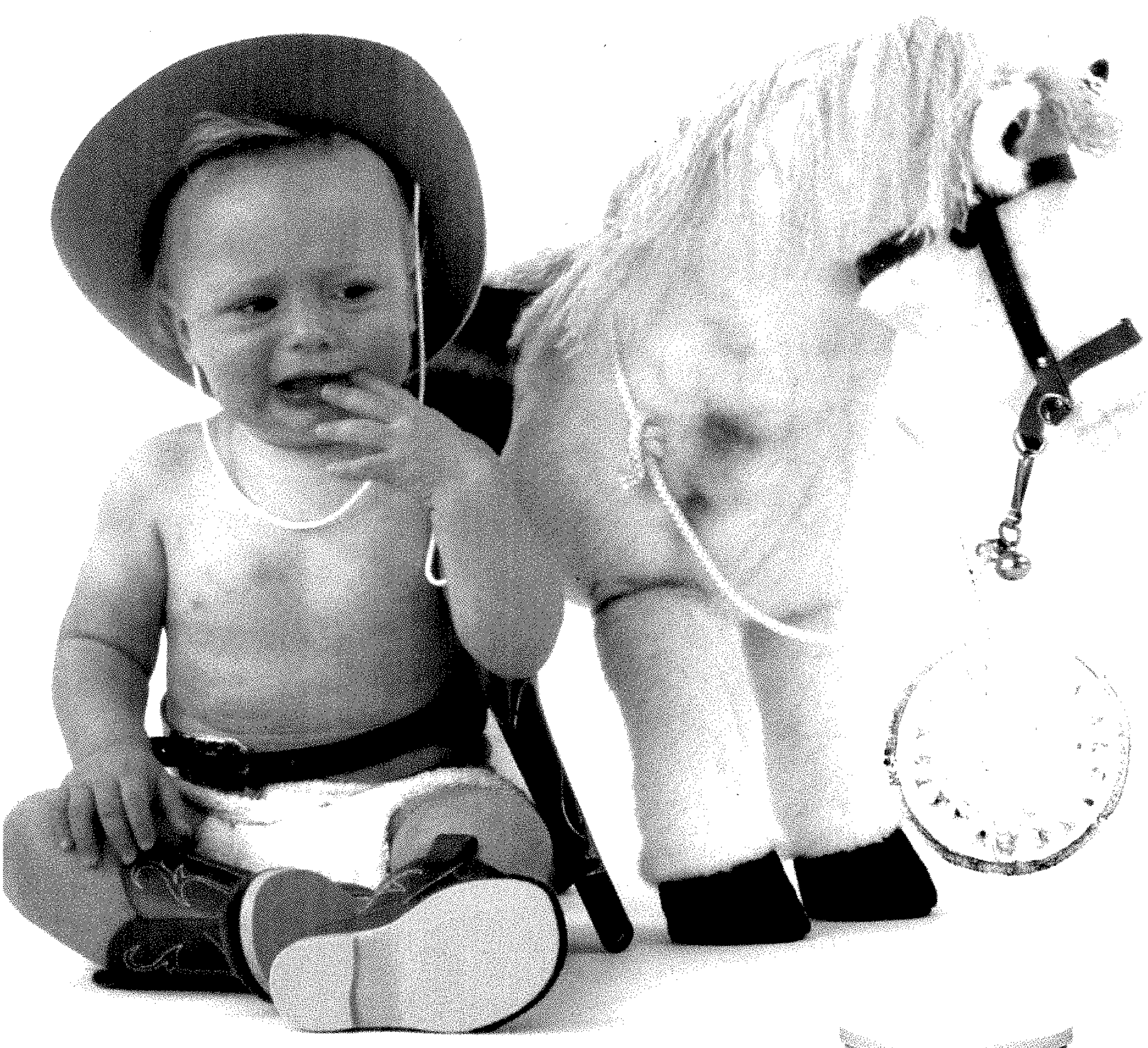

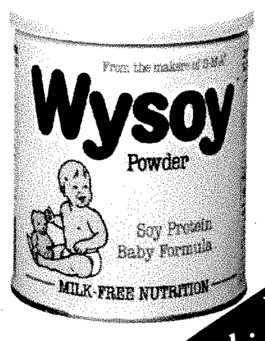

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ARCHIVES OF DISEASE IN CHILDHOOD

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intramuscular injection.

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te overdosage is unlikely and does not
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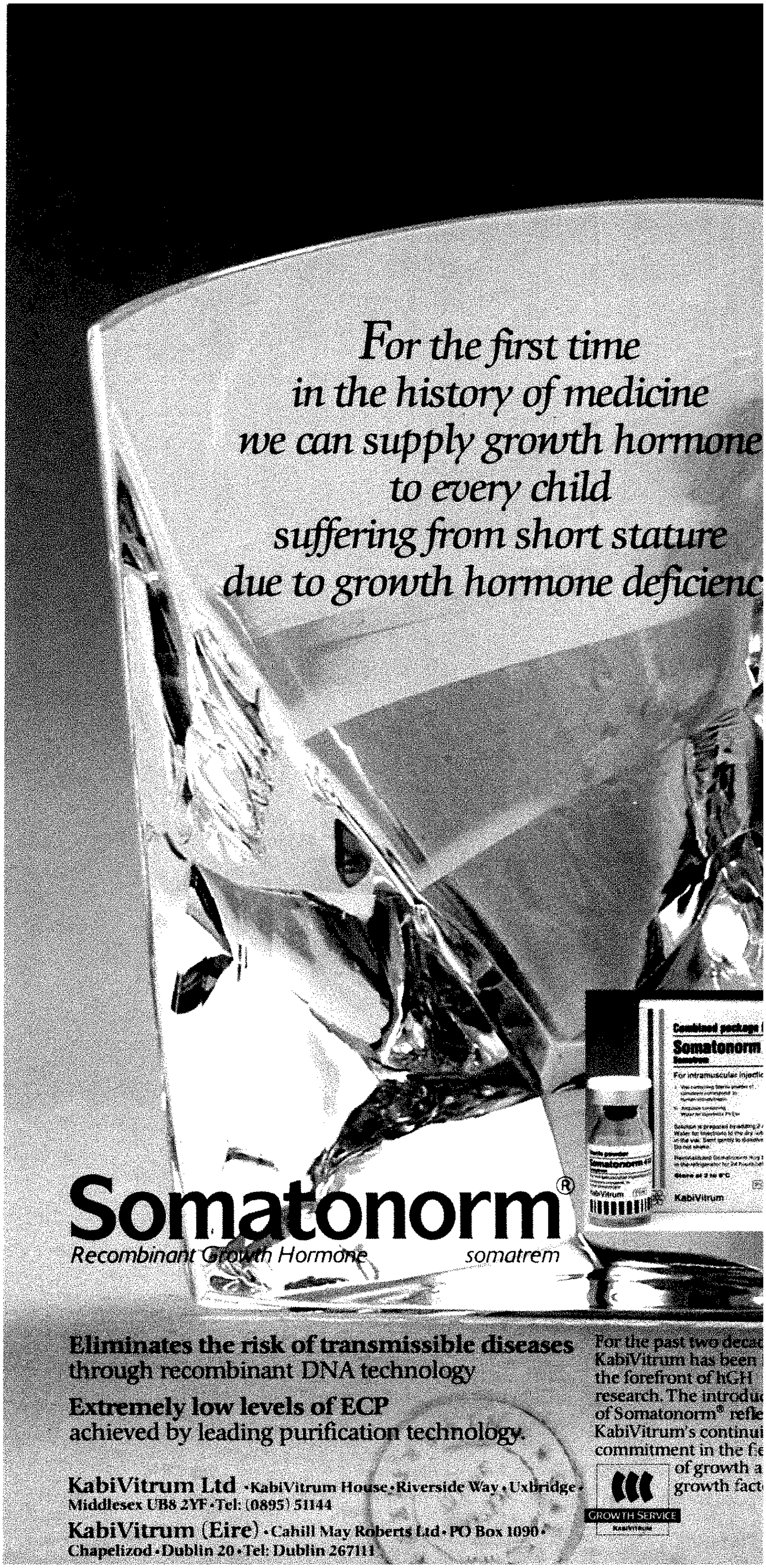
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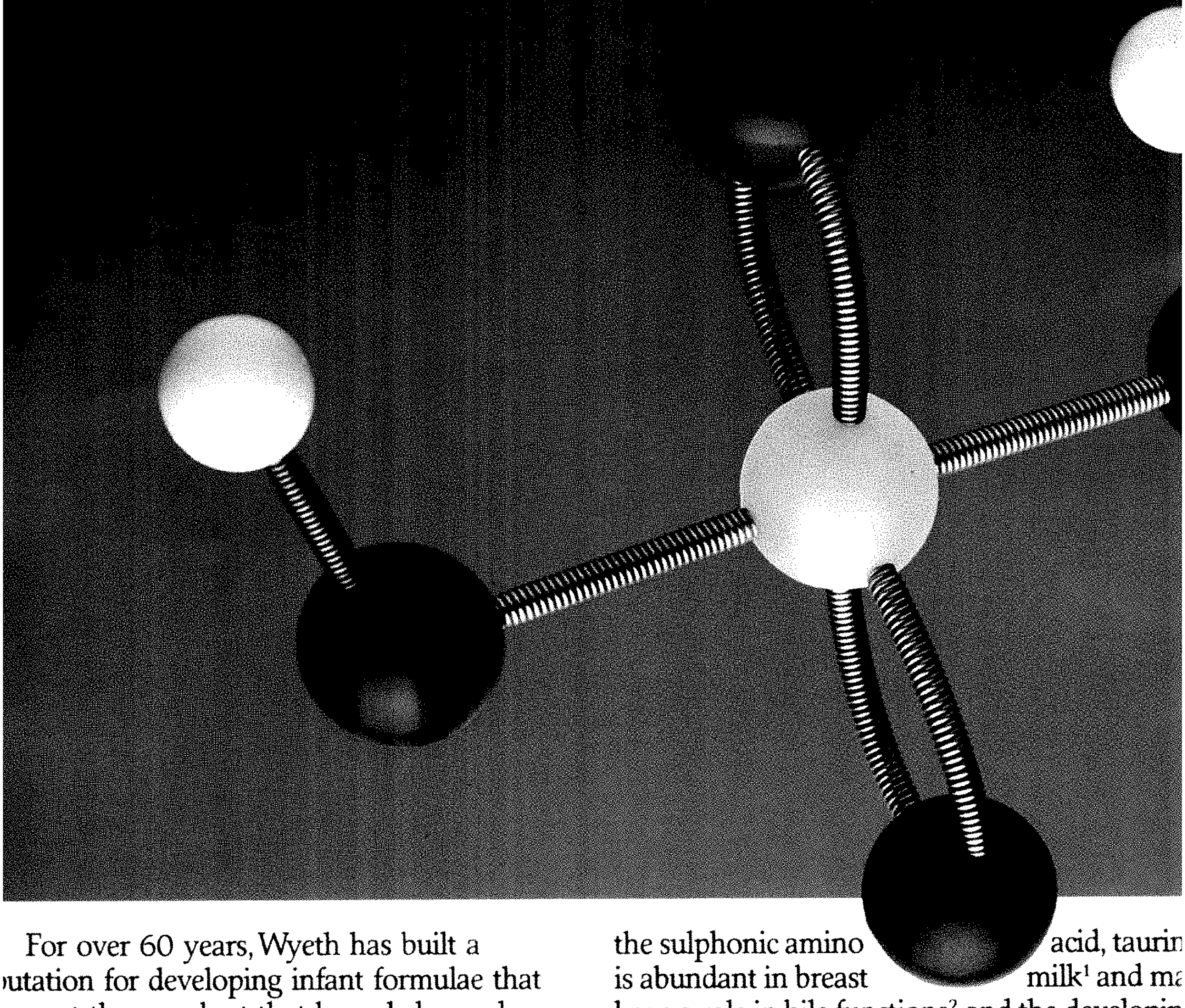

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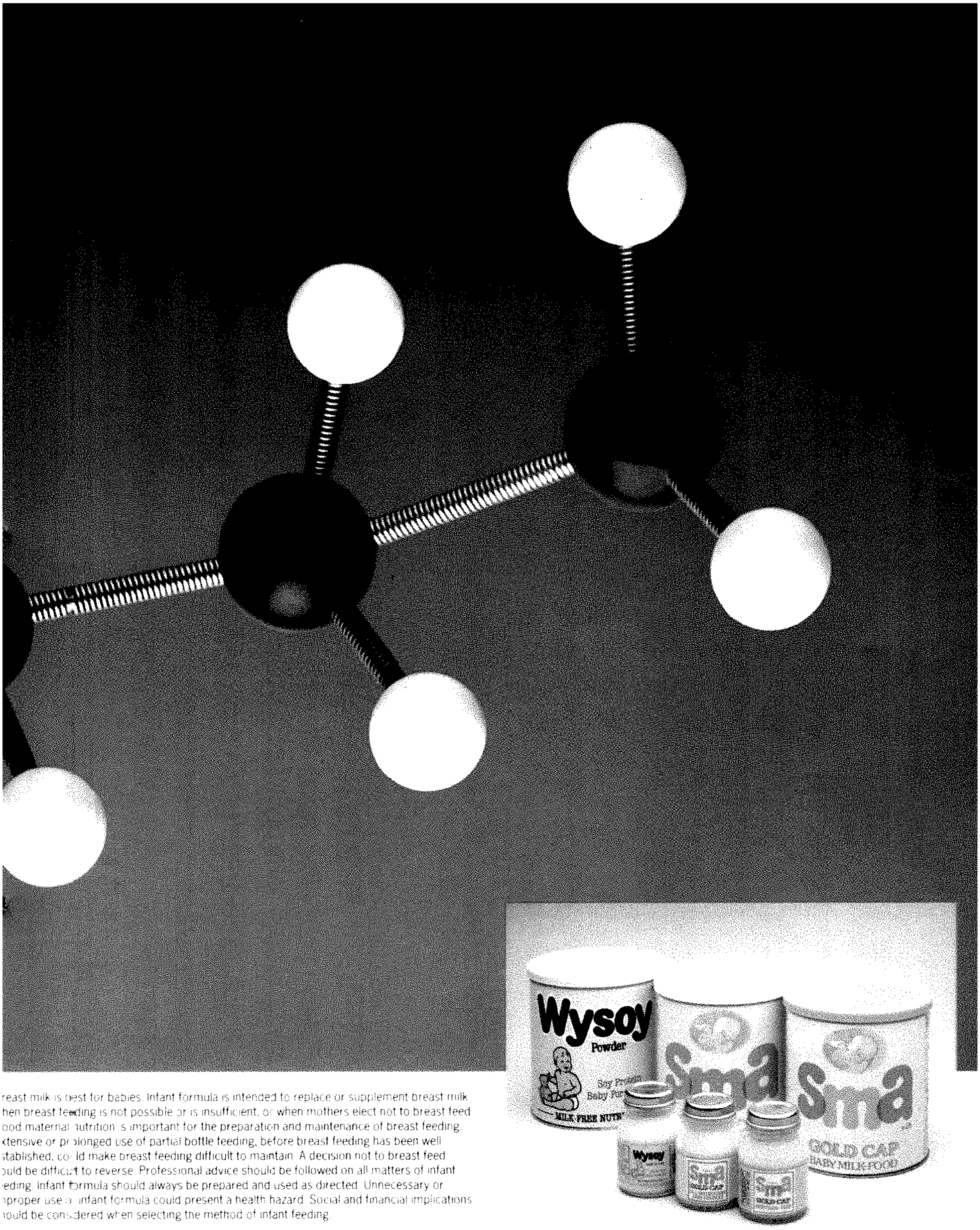

reast milk is best for babies. Infant formula is intended to replace or supplement breast milk hen breast feeding is not possible or is insufficient, or when mothers elect not to breast feed ood maternal nutrition is important for the preparation and maintenance of breast feeding. xtensive or prolonged use of partial bottle feeding, before breast feeding has been well stablished, could make breast feeding difficult to maintain. A decision not to breast feed ould be difficult to reverse. Professional advice should be followed on all matters of infant eding. Infant formula should always be prepared and used as directed. Unnecessary or proper use of infant formula could present a health hazard. Social and financial implications ould be considered when selecting the method of infant feeding.

ferences: 1. Rassin D.K., Sturman J.A., Gaull G.E. (1978). Taurine and other free amino acids milk of man and other mammals. Early Human Development 2/1, 1. **2.** Jaavenpaa A.L., asin D.K., Kuitunen P., Gaull G.E., Raiha N.C.R. (1983). Feeding the low birthweight infant: Diet influences bile metabolism. Paediatrics 72, 677. **3.** Sturman J.A., Gaull G.E. (1976). urine in the brain and liver of the developing human and rhesus monkey. In: Huxtable R., arbeau A. (eds). Taurine. Raven Press, New York, pp 73-84. **4.** Sturman J.A., Wen G.Y., isniewski H.M., Neuringer M.D. (1984). Retinal degeneration in primates raised on synthetic fant formula. Int. J. Dev. Neurosci. 2, 121. **5.** Huxtable R.J., Sebring L.A. (1983). Cardiovascular ctions of taurine. In: Kuriyama K., Huxtable R.J., Iwata H. (eds). Sulfur Amino Acids: iochemical and Clinical Aspects. Alan R. Liss, New York, pp 5-37.

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Date of Preparation: January 1986
References: 1. Corcoran, J.S. and Yudkin, J.S. Diabetic Medicine, 1985, **2**, 131-133. 2. Fineberg, S.E. *et al*. Diabetologia, 1983, **25**, 465-469.

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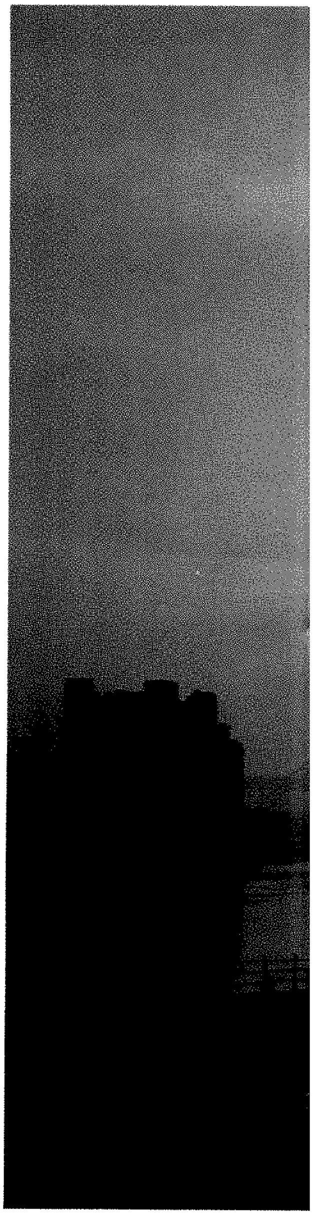

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:hieved. (Usually within the range
)-30mg/kg body weight per day)
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›ight per day in severe cases may be
creased up to 40mg/kg day Increases
›ove this only if plasma valproic acid
vels. clinical chemistry and haematological
ırameters can be monitored **Combined**
ıerapy It may be necessary to raise the dose
ıen used with anticonvulsants which induce
er enzyme activity Dosage of barbiturates
ould be reduced if sedation is observed
›timum dosage is mainly determined by
ızure control and routine measurement of
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sfunction including hepatic failure resulting
fatalities has occurred in patients whose
›atment included valproic acid or sodium
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› first 6 months of therapy Clinical symptoms are
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the early stages of hepatic failure The
set of an acute illness especially
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:lude symptoms of vomiting.
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ın indication for withdrawal of medication
ncreatitis. tremor. weight gain transient
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ıy potentiate monoamine oxidase inhibitors and
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›blem **Women of Childbearing Age** Valproic
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Annotations

Pharmacological manipulation of the ductus arteriosus

Physiological considerations

The postnatal rise in blood oxygen tension is widely recognised as the trigger to closure of the ductus arteriosus. The prostaglandins are increasingly recognised as the mediators of this phenomenon.[1] One suggested mechanism is that increased oxygen tension may promote the conversion of arachidonic acid to prostaglandin $F_{2\alpha}$, which is known to be present in ductus arteriosus tissue and is a ductus constrictor. Another is that patency of the fetal ductus arteriosus may be actively sustained by intramural prostaglandin E_2 (PGE_2) and that postnatal exposure to oxygen reduces the responsiveness of the ductus to PGE_2. There are certain clinical conditions in which the oxygen trigger does not seem to operate fully—for example, the ductus arteriosus often closes in congenital right heart obstructive lesions despite severe hypoxaemia, while it often remains patent in premature infants despite normal blood oxygen tensions. Treatment has been directed on the one hand towards the use of the E type prostaglandins to maintain ductus arteriosus patency and on the other towards the drug inhibition of prostaglandin synthesis to encourage ductus constriction. Indomethacin has been the drug most widely used as a prostaglandin synthetase inhibitor.

Management of patent ductus arteriosus in the premature infant

The demonstration that administration of indomethacin could achieve closure of patent ductus arteriosus in premature infants led to a major collaborative randomised trial in the United States.[2] Approximately 20% of 3559 infants weighing 1750 g or less met the criteria of having a 'haemodynamically significant' patent ductus arteriosus, including the need for ventilatory support. Infants were excluded if there was poor renal function, a bleeding tendency, or necrotising enterocolitis. Approximately 10% of the whole group of infants consequently entered the trial.

All infants were given conventional medical treatment, including fluid restriction and diuretics. Indomethacin was either given at the beginning of 'usual medical therapy' or after 36–48 hours of treatment with placebo or not at all, the groups having been randomised and the physicians 'blinded'. Surgical ligation of the patent ductus arteriosus was undertaken if medical treatment failed in any of the groups.

At 48 hours after treatment 79% of infants who had received indomethacin no longer had a 'haemodynamically significant' patent ductus arteriosus compared with 28% of those who had received placebo. The ductus arteriosus reopened in 26% of those who received indomethacin but it subsequently closed again in most of them. Overall, permanent closure of the ductus arteriosus occurred without the need for surgery in 79% of the infants who received indomethacin and in 35% of those who received placebo. In infants whose birth weight was less than 1000 g the closure rate associated with treatment with indomethacin was three times the spontaneous closure rate but the incidence of indomethacin failures was also slightly higher than in infants weighing more than 1000 g.

The overall mortality did not differ significantly whether infants were given usual medical treatment with indomethacin initially or later or whether they proceeded to surgical ligation of the ductus arteriosus having been in the placebo or the indomethacin group. The surgical group, however, had a higher complication rate, especially pneumothorax and retrolental fibroplasia, and the infants who were given indomethacin as part of the initial treatment had a higher incidence of bleeding than those to whom it was given only when usual medical treatment had failed. Bronchopulmonary dysplasia and necrotising enterocolitis had a similar incidence in each of these groups. In a follow up evaluation at the age of 1 year there were no significant differences between the groups in terms of the proportion of infants with poor outcome.[3]

Conclusions. There seems to be some merit in using intravenous indomethacin in those infants with a notable patent ductus arteriosus who do not respond to 36–48 hours of fluid restriction and diuretics and in whom there is no contraindication to its use.

Approximately one quarter of all infants with a haemodynamically significant patent ductus arteriosus would then probably require surgical closure compared with two thirds if indomethacin was not used. The multi-centre study did not report whether the results varied from one centre to another. The timing of surgical closure of the ductus would probably have been based on the individual clinical assessment of each infant and might conceivably have influenced the outcome in the various centres. Small randomised studies have been reported in which infants were given indomethacin as a prophylactic measure.[4] Although a lower incidence of subsequent appreciable shunting was shown, there were more complications, and the overall benefits of this strategy must remain speculative.

Principles of management. A firm policy will often depend on the experience of the individual centre and the local surgical results. When optimal conditions prevail for both medical and surgical management it seems reasonable to use indomethacin after 36–48 hours of fluid restriction, diuretics, and other routine measures. The recommended initial intravenous dose is 0·2 mg/kg body weight, repeated at 12 hourly intervals for a total of three doses. The second or third dose should not be given if contraindications develop or if there is evidence that complete closure of the ductus arteriosus has already occurred. In those infants who are 8 days or older the second and third doses of indomethacin may be increased to 0·25 mg/kg body weight because there is evidence that indomethacin is metabolised more rapidly by the premature infant as postnatal age advances. If the patent ductus arteriosus remains significant early surgical ligation should be undertaken. If indomethacin induces 'closure' and the ductus then 'reopens' a further three doses of indomethacin may be tried before resorting to ligation. The good surgical results in the major cardiac surgical centres justify fairly early referral for ligation.

Ductus dependent congenital heart disease

The E type prostaglandins: pathophysiological considerations. In early clinical studies infusions of either prostaglandins E_1 or E_2 (PGE_1 or PGE_2) were consistently effective in improving the oxygenation of neonates whose pulmonary blood flow depended on patency of the ductus arteriosus.[5–7] Infusions of PGE_1 also proved helpful in neonates with interrupted aortic arch, juxtaductal coarctation of the aorta and hypoplastic left heart syndrome,[8] and, more recently, critical aortic stenosis; ductus patency allowed the descending aorta and kidneys to be perfused from the pulmonary artery. The other application of treatment with prostaglandin E is the presence of complete transposition of the great arteries when interatrial mixing is poor, either before or after balloon atrial septostomy.[7] The increased flow through the ductus arteriosus from the aorta to the pulmonary artery then results in an increase in pulmonary blood flow and an increased pulmonary venous return to the left atrium. The left atrial pressure rises, encouraging the flow of oxygenated blood across the interatrial communication into the right heart and the systemic circulation.

Clinical evaluation of treatment with prostaglandin. An extensive assessment of the use of infusion of PGE_1 in treating infants with ductus dependent congenital heart disease was undertaken in a collaborative clinical trial in the United States involving 492 infants.[9 10] In almost all the cases in the study the infusion was continued for no more than several hours, the objective being to stabilise the infant in preparation for emergency palliative surgery. PGE_1 (rather than PGE_2) was chosen for the trial for theoretical reasons, although PGE_2 had seemed equally effective. The earlier reports and the collaborative study emphasised the use of infusion of PGE_1 or PGE_2 for a period of a few hours before emergency surgery. Longer term infusion was initially reported in preterm infants, but enthusiasm for its use has probably been limited partly by practical considerations as well as by an appreciable incidence of side effects.[6 10] The use of an oral preparation of PGE_2 has simplified long term administration.[11 12]

In infants with a ductus dependent pulmonary circulation a single oral dose of PGE_2 caused an increase in arterial oxygen content similar to that reported in the US collaborative study when intravenous infusion of PGE_1 was used. Arterial oxygen saturation and plasma PGE_2 concentration reached similar values whether PGE_2 was given orally or by intravenous infusion. These values increased within 15–30 minutes after an oral dose, implying rapid absorption from the alimentary tract. A larger dose caused a proportionately greater increase in plasma PGE_2 concentration, confirming that absorption was efficient. Higher plasma PGE_2 concentrations, however, were not usually associated with better blood oxygenation, probably because the ductus had been fully dilated by the lower dose. These observations have helped to rationalise both the route of administration and the appropriate dosage.

Hourly administration of oral PGE_2 is necessary to maintain arterial oxygenation at satisfactory levels for the first week or two. Subsequently, the dosage or its frequency can be reduced. The ductus arteriosus did not remain patent if treatment with PGE_2 was stopped, even after many months of treatment, but in some infants it has been possible to lengthen the periods between doses to as much as every 4–6 hours to treat them at home. Long term treatment encouraged growth of the infants and of their pulmonary arteries, which seemed to be advantageous to the surgeons when they performed palliative shunts.

Complications of E type prostaglandins. The incidence of complications in the first 62 patients treated in Birmingham with PGE_2 (oral or intravenous, or both)[12] was compared with those reported in the US collaborative study in which intravenous PGE_1 was used.[10] Apnoea and cardiovascular complications were much less common during low dose treatment with PGE_2 than during infusion of PGE_1, but diarrhoea and mild fever were more common. Necrotising enterocolitis was a rare complication in both studies, usually related to cardiac catheterisation. Complications such as cortical hyperostosis, friability of the ductus arteriosus, or damage to pulmonary vascular smooth muscle have been described after long term treatment with PGE_1. None were seen in infants treated with long term PGE_2, probably having been avoided by the low dosage used in Birmingham.

Rationale of treatment with prostaglandin E. There are distinct advantages in using the oral preparation in preference to the intravenous one. It is easier to administer and its absorption and beneficial effects are rapid. It is particularly suitable for long term use and it has enabled most infants so treated to grow satisfactorily. There may also be an economic argument in favour of PGE_2: the cost of the intravenous preparation is one fifth the cost of PGE_1 and the daily cost of treatment with the oral preparation is only 14% the cost of an ampoule of PGE_1.

Treatment with oral PGE_2 is usually begun as soon as the diagnosis has been established by cross-sectional echocardiography. If a subsequent diagnostic cardiac catheterisation is to be performed it is better done when the neonate's oxygenation and metabolic state have been improved. Treatment may be begun in the neonatal unit before transferring the infant to the cardiac referral centre, preferably after consultation with the cardiologist because there are potential risks if infants with total anomalous pulmonary venous return or persistent fetal circulation are inadvertently given prostaglandin E.

The initial oral dosage of PGE_2 should be 20–25 μg/kg hourly, decreasing the dose frequency after the first week. When gastrointestinal absorption is expected to be poor, when oral treatment is ineffective, or if diarrhoea becomes troublesome an intravenous infusion should be begun in a dose of 0·003 μg/kg/min. Occasionally it is necessary to increase the infusion dose for a few hours and it is exceptional to have to use doses as high as 0·01 μg/kg/min. There seems to be little justification for the continued advocacy of doses as high as 0·05–0·10 μg/kg/min even if PGE_1 is used. Infants may be treated with oral PGE_2 for between one and four weeks initially, and then decisions should be made on an individual basis whether to proceed with surgery or to plan a longer course of treatment to encourage further growth.

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Guardians ad litem

Who are they?

The office of guardian ad litem is an ancient one; guardians have traditionally been appointed in court proceedings to safeguard the interests of children and mental patients. But from May 1984, in response to the Maria Colwell tragedy, the courts have been given new powers to appoint guardians ad litem to look after children's interests in care proceedings—where a local authority goes to the magistrates court for an order allowing it to take a child into care, usually because of neglect or ill treatment, or where parents apply to the magistrates to have a child in the care of the local authority returned to them.

Why were they needed?

The inquiry into Maria Colwell's death highlighted the fact that the interests of children and their parents often do not coincide. Parents are not parties to care proceedings—the two parties are the local authority and the child. Because they are not parties, parents until recently were denied legal aid. But solicitors acting on legal aid for the child did not always appreciate the possible conflict of interest between the child and his parents and too often took their instructions from the parents, as if they were the clients. The 1975 Children Act provided for local authorities to maintain panels of independent social workers to act as guardian ad litem to the child, and for parents, though not parties, to have legal aid to instruct their own, separate, solicitor. It took nearly 10 years for the new system to come into operation, but in the meantime, as a result of Law Society guidance, solicitors acting for children in care proceedings increasingly asked independent social workers to assist them, as happened in the Jasmine Beckford case, where the proceedings took place before the new system was brought into force.

The guardian ad litem's role

The roles of an independent social worker and of a guardian ad litem are, however, different. The solicitor can disregard the social worker's report or put it forward as he chooses, depending on whether it advances his case. The guardian ad litem, by contrast, is appointed by the court and is very much in control of the case. It is the guardian who instructs the solicitor on the child's behalf, carries out the investigation, and puts all the relevant circumstances before the court. Unlike independent social workers, guardians ad litem have the right to examine social services' and other records.

Selection and duties

Guardians ad litem, drawn from panels kept by local authorities, are trained social workers who are independent or employed by voluntary agencies or by other local authorities. As the report of the Jasmine Beckford enquiry points out, 'the leitmotif of modern child care law is preventive action.'[1] Local authorities have a general duty to provide support for children in their families, so as to lessen the need to take children into care. This overall preventive duty, however, is no part of the guardian ad litem's role. His task is to safeguard and promote the child's interests until adulthood, assist the court, and ascertain, and inform the court of, the child's wishes and feelings. He has a duty to 'so far as it is reasonably practicable, investigate all circumstances relevant to the proceedings' and, to do this, to 'interview such persons and inspect such records and obtain such professional assistance' as he thinks appropriate.

In the Beckford case the magistrates were not shown a crucial paediatric radiologist's report. Had a guardian ad litem been appointed, says the panel's report, 'Dr Levick's report would never have suffered the fate of courtroom confusion, or subsequent interment in a departmental file.'

It is up to the guardian, however, whether he thinks it relevant to the proceedings and appropriate to interview a paediatrician who has been involved with the child. Some paediatricians have complained that in some cases guardians have not approached them and have also bypassed social workers and health visitors who have known the family intimately. The blue book prepared by the Department of Health and Social Security (DHSS) states: 'He (the guardian) should not overlook other adults with whom the child has established a relationship or who may be able to comment on his needs. Legal aid will usually be available to pay for expert advice or reports from specialists such as educational psychologists, doctors or child psychiatrists.'[2] It is certainly up to the guardian what weight to attach to a paediatrician's view on whether the child should be returned to his parents when he comes to write his report for the court.

If the child and the guardian disagree

What if the child disagrees with what the guardian ad litem believes to be in his best interests? The child, for instance, may not want to be taken into care, while the guardian ad litem may favour a care order. If the solicitor thinks the child is old enough and has sufficient understanding he must take instructions from the child. From that point, the solicitor and the guardian ad litem cease to work together, and the solicitor may challenge the guardian ad litem's report by calling an independent social worker as witness. In these circumstances a paediatrician who had not been approached by the guardian might be called as a witness by the child's solicitor.

What can paediatricians do?

DHSS advice to a paediatrician who feels his possible contribution has been overlooked by a guardian ad litem is first to approach the guardian offering to assist with the investigation. If the offer is turned down he may wish to get in touch with the child's solicitor or make it known to the clerk of the court that he feels he has an interest in the case. A DHSS spokesman has pointed out that the guardian has access to social services records and if a paediatrician has been part of a child abuse team his views may already be noted in those records.

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Prognostic value of different staging systems in neuroblastomas and completeness of tumour excision

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SUMMARY Two hundred and fifty three patients were retrospectively assigned to eight different staging systems proposed for neuroblastomas, and the prognostic value of each staging system was evaluated individually. The ability of each system to predict prognosis was compared with the others and the system proposed by Evans *et al* found to be the best predictor, even better than the recently proposed Tumour-Nodes-Metastases staging system. This is probably due to the fact that factors other than the resectability of the tumour play a major role in the survival of these children. Age was found to have independent prognostic significance whatever staging system was used.

The vagaries of the natural history of neuroblastomas are notorious, and because of this various staging systems have been proposed in estimating the prognosis for children with this tumour, mostly based on the extent of the disease, the surgical resectability, the pattern of metastatic spread, and, in some cases, the degree of histologic differentiation. The staging system of Evans *et al*[1] is the most widely adopted, although the system proposed by Pinkel *et al*[2 3] is also widely used and recently a Tumour-Nodes-Metastases (TNM) staging system has been devised under the auspices of the International Union against Cancer.[4]

The aims of this study were to restage retrospectively an unselected patient population comprising all children with neuroblastoma in Denmark during the period 1943–80 according to the various staging systems proposed, to compare the prognostic value of the different systems, and to evaluate the role of surgical excision of the primary tumour on the prognosis.

Material and methods

The patients comprised 255 cases of neuroblastoma treated in Denmark during the period 1943–80. Of these, 237 had been proved histologically. In the remaining 18 the case history pointed clearly to neuroblastoma but either the histological diagnosis was inconclusive—that is, suggestive of neuroblastoma—and could not be re-examined (13 cases) or no histological diagnosis had been made and the diagnosis was based on either raised urinary excretion of 3-methoxy-4-hydroxymandelic acid (three cases) or orbital metastases and tumour abdominis (two cases). These 18 cases were staged according to Evans *et al*[1] as follows: stage I: 0 cases; stage II: two; stage III: two; stage IV: 12; stage IV-S: one; stage unknown: one, as the hospital record of a child with the histological diagnosis suggestive of neuroblastoma had disappeared. One child died at home without having been admitted to hospital and thus could not be staged; the autopsy revealed neuroblastoma. It was therefore possible to stage the extent of the disease according to the various staging systems for 253 cases only. Studies from part of this patient population have been published elsewhere.[5]

Patients without evidence of the disease two years after diagnosis were considered cured. The tumours were staged retrospectively according to the following systems: Evans *et al*,[1 6] Pinkel *et al*,[2 3] Sandstedt *et al*,[7] Cohen,[8] James,[9] Thurman and Donaldson,[10] the TNM clinical stage grouping,[4] and the TNM post surgical histopathological stage grouping.[4] It should be mentioned that for staging purposes investigations not performed were considered negative. The different staging systems are as follows.

Evans *et al.*[1 6]

Stage I

Tumours confined to the organ or structure of origin.

Stage II
Tumours extending in continuity beyond the organ or structure of origin but not crossing the midline. (Regional lymph nodes on the homolateral side may be involved. All intraspinal tumours are included unless the extraspinal portion of the tumour crossed the midline. For tumours arising in midline structures—for example, the organs of Zuckerkandl—penetration beyond the capsule and involvement of lymph nodes on the same side shall be considered stage II. Bilateral extension of any sort shall be considered stage III.)
Stage III
Tumours extending in continuity beyond the midline. (Regional nodes bilaterally may be involved.)
Stage IV
Remote disease involving skeleton, organs, soft tissues, or distant lymph node groups (see stage IV-S).
Stage IV-S
Patients who would otherwise be classed as stage I or II but who have remote disease confined only to one or more of the liver, skin, or bone marrow (without radiographic evidence of bone metastases on complete skeletal survey).

Pinkel *et al.*[2 3]
Stage I
Localised, complete resected tumour.
Stage IIA
Localised, resected, but possibly residual microscopic tumour.
Stage IIB
Localised tumour, partially or not resected.
Stage IIIA
Regional or systemic spread of disease without involvement of bone or bone marrow.
Stage IIIB
Same as stage IIIA, but evidence of a single, localised destructive lesion of bone; no involvement of bone marrow.
Stage IIIC
Generalised tumour in bone or bone marrow, or both.

Sandstedt *et al.*[7]
Stage A
Localised, well incapsulated tumour.
Stage B
Tumours infiltrating surrounding organs or regional lymph nodes.
Stage C
Tumours with metastases to distant lymph nodes or other organs, or both.

Stage IV-S
The same definition as in the classification of Evans *et al* (see above).

Cohen.[8]
Stage 1
Disseminated disease. Cases showing histological evidence of involvement of bone marrow or clinical or radiological evidence of bony or periorbital metastases.
Stage 2
Hepatic disease. Cases presenting with gross hepatomegaly without other evidence of metastatic involvement, with or without a discoverable primary tumour. Liver biopsy confirms that the liver is diffusely involved by undifferentiated neuroblastoma.
Stage 3
Peripheral disease. These cases present with superficial nodules, which are shown on biopsy examination to be undifferentiated neuroblastoma tissue. A primary tumour may or may not be detectable. Fresh nodules continue to occur for a limited time and may be cutaneous, subcutaneous, or subfascial, within one of the muscle bellies. They are usually small, encapsulated nodules that are readily dissected out for biopsy examination.
Stage 4
Infiltrative disease. In these cases the tumour is usually large and vascular. Because of its lack of a complete capsule it is invariably irremovable. There is usually pronounced involvement of regional lymph nodes, extending well up around the great vessels.
Stage 5
Encapsulated tumours. Such tumours can always be totally or subtotally removed.
Stage 6 and Stage 7
These comprise differentiated tumours (grade I or II of Beckwith and Martin[11]) and neuroblastoma in situ[12] but are excluded from this study as no attempt has been made to grade the tumours histologically in this study and as cases of neuroblastoma in situ possibly represent a variation in the normal morphogenesis of the adrenal gland.[13]

James.[9]
Stage I
Localised and resectable.
Stage II
Regional and unresectable.
Stage III
Generalised and without involvement of bone or marrow.

Stage IV
Generalised and with involvement of bone or bone marrow.

Thurman and Donaldson.[10] Excludes all children under 1 year of age.
Stage I
Localised and totally resectable.
Stage II
Regional, non-resectable.
Stage III
Generalised and with involvement of bone marrow.
Stage IV
Generalised and with involvement of bone.

Stages I and II are originally subclassified according to the differentiation of the tumours, which as previously mentioned is not possible in this study. Similarly, the original proposal that stage I tumours automatically be reclassified to stage II if excretion of catecholamine remains high three months after removal of the tumour is not possible for all tumours in this study as the urinary excretion of 3-methoxy-4-hydroxymandelic acid was not analysed in all the patients. The proposal is therefore excluded from this study.

TNM clinical stage grouping.[4]
Stage I
Primary tumour 5 cm or less in its greatest dimension; no evidence of involvement of regional lymph nodes, or the minimum requirements to assess the regional lymph nodes cannot be met. No evidence of distant metastases.
Stage II
Primary tumour more than 5 cm but not more than 10 cm in its greatest dimension. No evidence of involvement of regional lymph nodes, or the minimum requirements to assess the regional lymph nodes cannot be met. No evidence of distant metastases.
Stage III
Primary tumour in stage I or II, but evidence of involvement of regional lymph node *or* primary tumour is more than 10 cm in its greatest dimension. The regional lymph nodes may or may not be involved. No evidence of distant metastases.
Stage IV
Primary tumour single, irrespective of its greatest dimension. Regional lymph nodes may or may not be involved. Evidence of distant metastases.
Stage V
Multicentric tumours occurring simultaneously. Regional lymph nodes may or may not be involved. Distant metastases may or may not be present.

TNM post surgical histopathological stage grouping.[4]
Stage I
Excision of tumour complete and margins histologically free. No evidence of tumour can be found on histological examination of regional lymph nodes or the extent of invasion cannot be assessed—that is, no surgical excision of the regional lymph nodes performed or inadequate information on the pathological findings. No evidence of distant metastases.
Stage II
Excision of tumour complete and margins histologically free. Evidence of invasion of regional lymph nodes, involved nodes considered to be completely resected, or the extent of invasion cannot be assessed (see above). No evidence of distant metastases.
Stage IIIA
Evidence of microscopic residual tumour. No evidence of tumour found on histological examination of regional lymph nodes, or evidence of invasion of regional lymph nodes, involved nodes considered to be completely resected, or the extent of invasion cannot be assessed (see above). No evidence of distant metastases.
Stage IIIB
Evidence of macroscopic residual tumour or grossly incomplete excision or primary tumour. Regional lymph nodes may or may not be completely resected *or* excision of tumour complete or with evidence of microscopic residual tumour, but evidence of invasion of regional lymph nodes, involved nodes considered to be incompletely resected. No evidence of distant metastases.
Stage IV
Primary tumour may or may not be resected. Regional lymph nodes may or may not be involved (and completely or incompletely resected). Evidence of distant metastases.
Stage V
Evidence of multicentric tumour. Regional lymph nodes may or may not be involved. Distant metastases may or may not be present.

In the TNM post surgical histopathological stage grouping[4] the operations performed on the primary tumour are defined as follows. pTO: No evidence of tumour found on histological examination of specimen. pT1: Excision of tumour complete and margins histologically free. pT3a: Evidence of microscopic residual tumour. pT3b: Evidence of macroscopic residual tumour. pT3c: Grossly incomplete excision. The prefix y to the above mentioned categories indicates secondary operation. Thus only pT1, ypT0, ypT1, pT3a, ypT3a, pT3b, and ypT3b could be assigned as tumour excision in evaluating the role of surgery in patients with neuroblastoma.

The tumours were classified in each staging system, one by one, by carefully reviewing the surgical notes of each patient as well as the physical examination and diagnostic studies at the time of diagnosis.

The initial statistical analysis of the 253 patients consisted of calculation of survival curves and simple statistics on these. The log rank test was used to compare survival curves drawn by the actuarian (decrement) method of Kaplan-Meier. Each of the staging systems was evaluated individually for prognostic significance and logistic regression analysis[14] used to detect the effect of each staging in the different systems on the survival after adjustment for other prognostic factors (age at diagnosis and treatment).

Results

Figure 1 shows the survival curves in the different stages proposed by Evans *et al.*[1 6] The prognosis gets progressively worse from stage I to stage IV with stage IV-S lying between them. The differences in survival between the different stages are significant (p=0·0001).

Figure 2 shows the survival curves in the different stages proposed by Pinkel *et al.*[2 3] The prognosis gets progressively worse from stage I to stage IIIA (p=0·0001), whereas the prognosis for stages IIA and IIB and for stages IIIA, IIIB, and IIIC are not significantly different.

Figure 3 shows the survival curves in the different stages proposed by Sandstedt *et al.*[7] The prognosis gets progressively worse from stages A to C with stage IV-S lying between them. The differences in survival between the different stages are significant (p=0·0001).

Figure 4 shows the survival curves in the different stages proposed by Cohen.[8] The prognosis gets progressively better from stage 1 to 5, with stages 2 and 3 lying between them. The difference between stage 1, stages 2 and 3, stage 4, and stage 5 is significant (p=0·0001), whereas the difference between stages 2 and 3 is not significant.

Figure 5 shows the survival curves in the different stages proposed by James.[9] The prognosis gets progressively worse from stage I to stage III (p=0·0001), whereas the difference between stages III and IV is not significant.

Figure 6 shows the survival curves in the different stages proposed by Thurman and Donaldson.[10] The prognosis gets progressively worse from stage I to stage III (p=0·0001), whereas the difference between stages III and IV is not significant.

Figure 7 shows the survival curves in the different

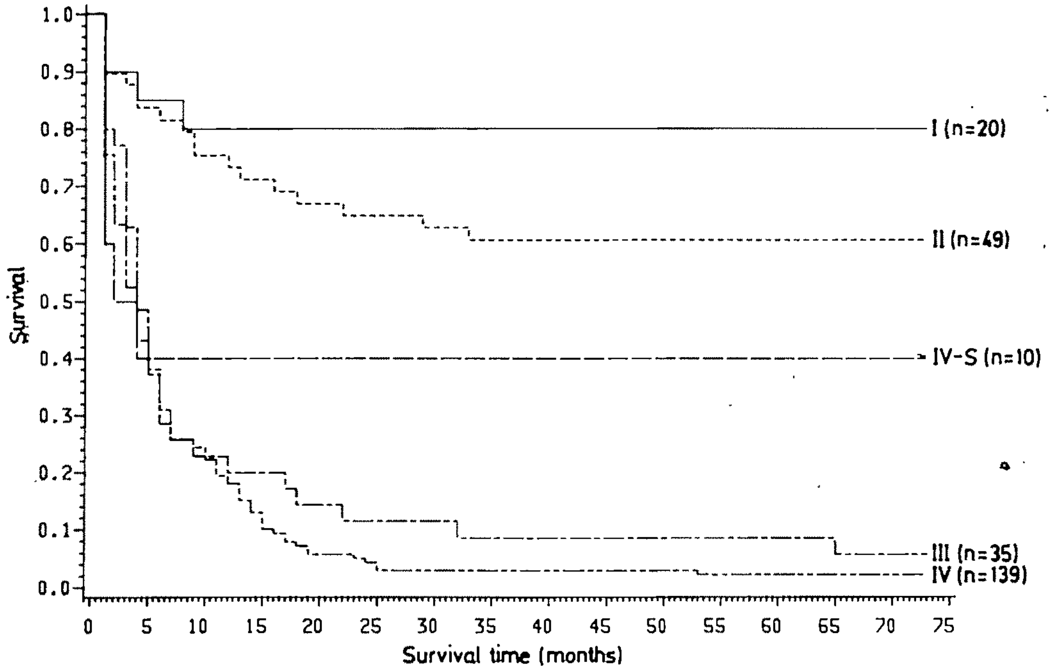

Fig. 1 *Survival in the different stages as proposed by Evans* et al *by Kaplan-Meier plot (the decrement method).*

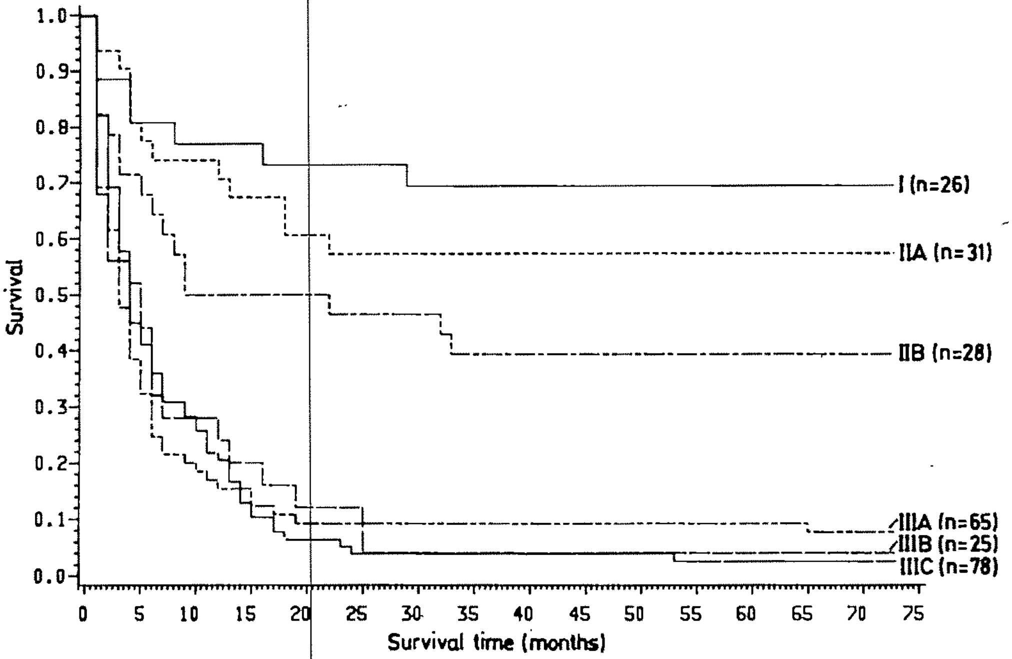

Fig. 2 *Survival in the different stages as proposed by Pinkel* et al *by Kaplan-Meier plot (the decrement method).*

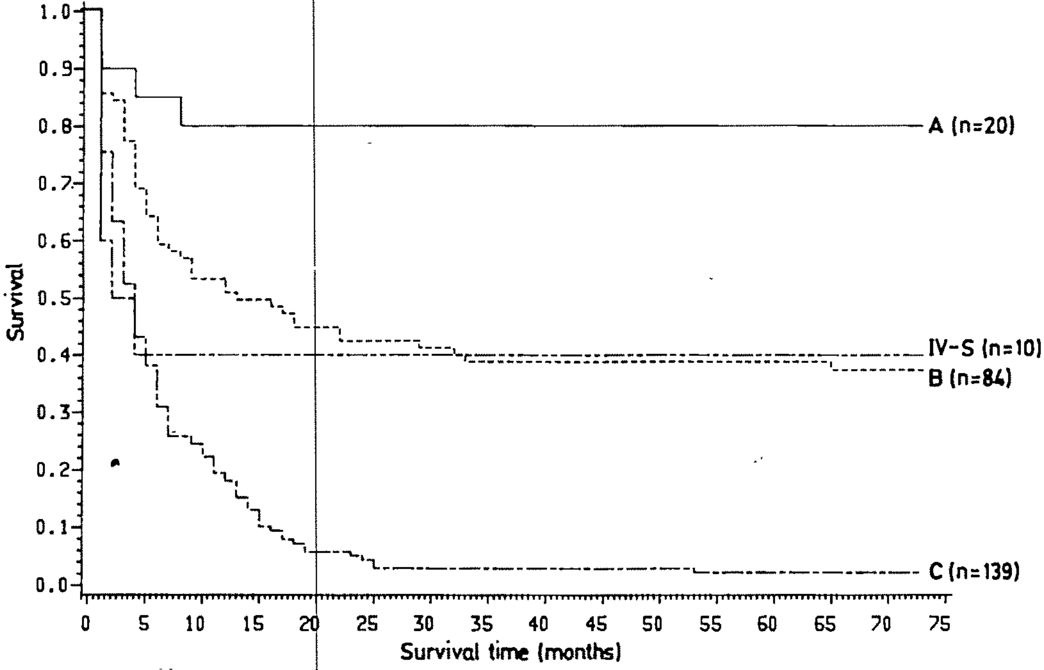

Fig. 3 *Survival in the different stages as proposed by Sandstedt* et al *by Kaplan-Meier plot (the decrement method).*

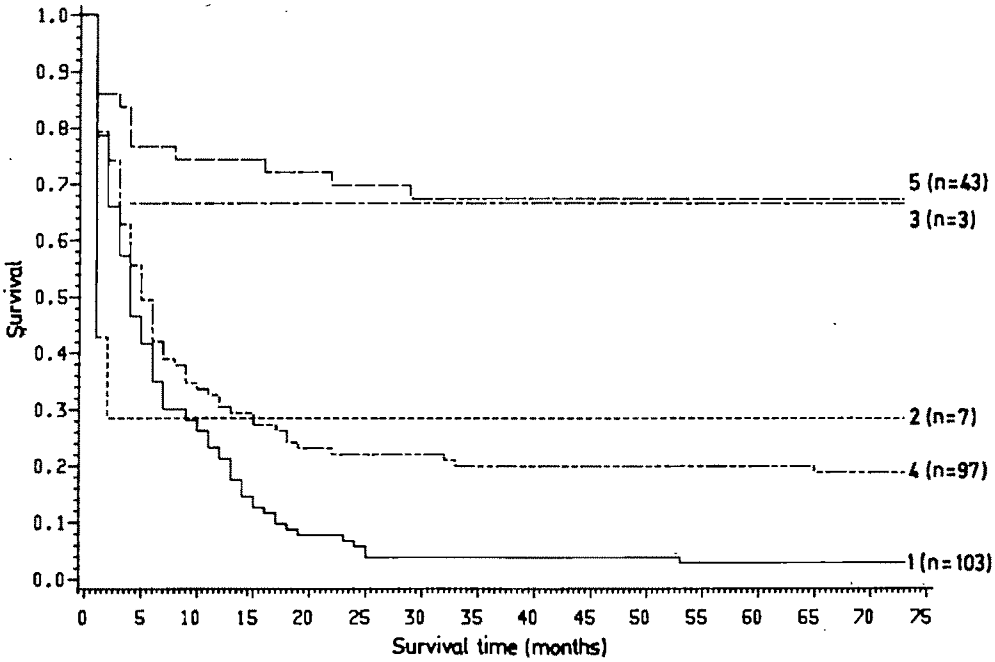

Fig. 4 *Survival in the different stages as proposed by Cohen by Kaplan-Meier plot (the decrement method).*

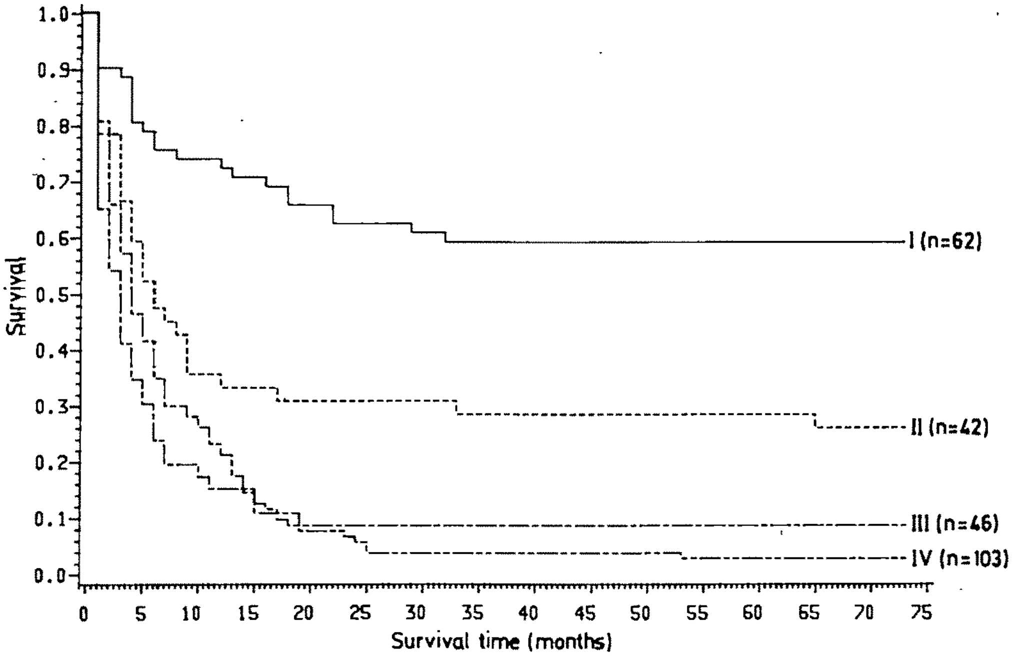

Fig. 5 *Survival in the different stages as proposed by James by Kaplan-Meier plot (the decrement method).*

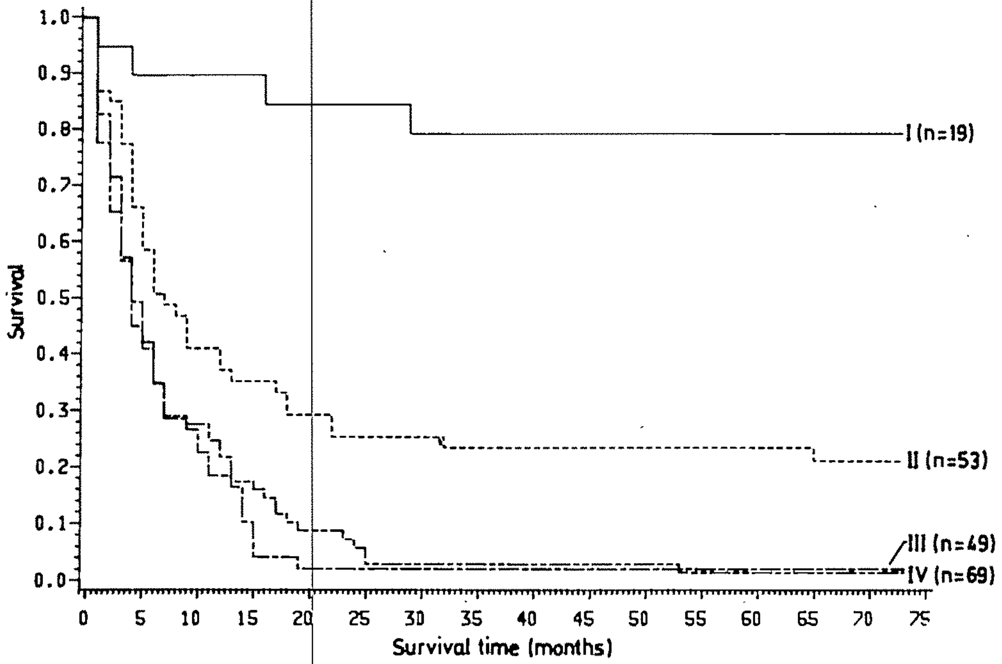

Fig. 6 *Survival in the different stages as proposed by Thurman and Donaldson (excluding children aged under 1 year) by Kaplan-Meier plot (the decrement method).*

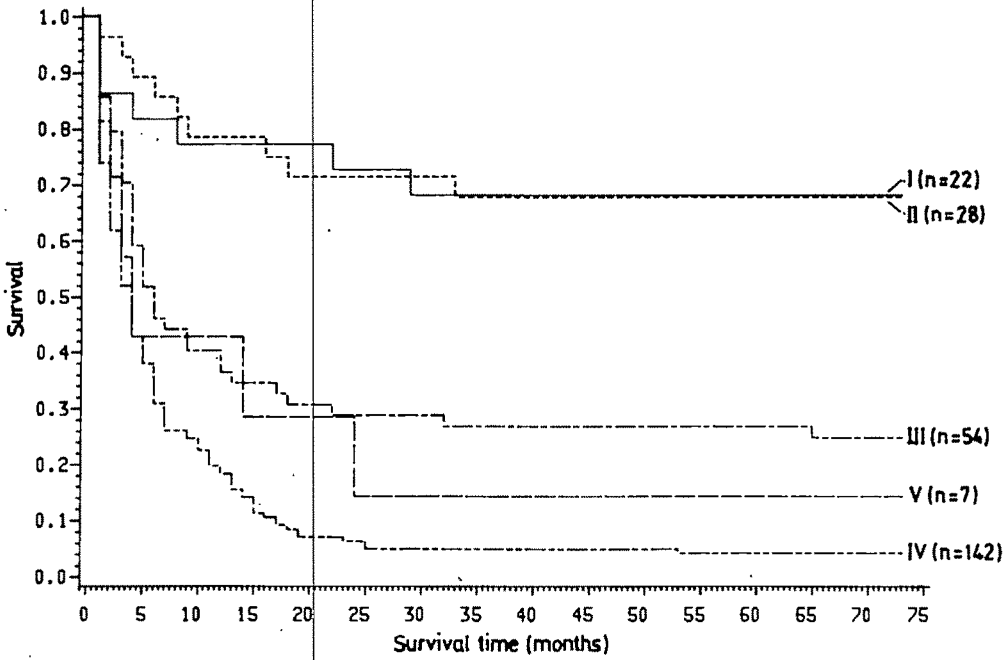

Fig. 7 *Survival in the different stages of the TNM clinical stage grouping by Kaplan-Meier plot (the decrement method).*

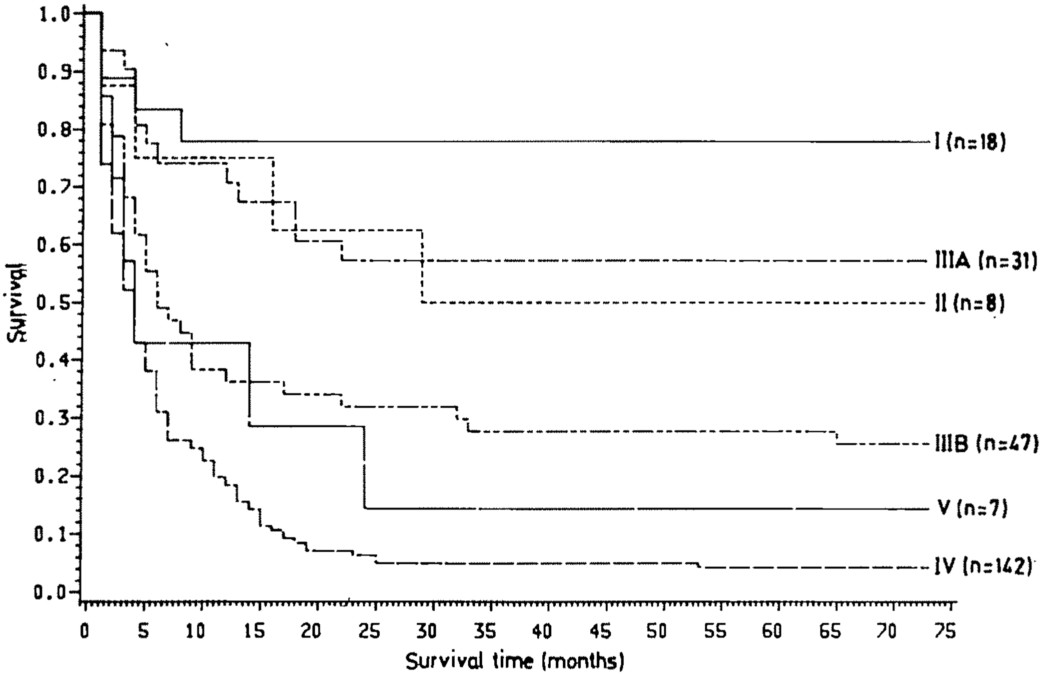

Fig. 8 *Survival in the different stages of the TNM post surgical histopathological stage grouping by Kaplan-Meier plot (the decrement method).*

stages of the TNM clinical stage grouping.[4] The prognosis gets progessively worse from stage I to stage IV ($p=0\cdot0001$), whereas the differences between stages I and II and between stages IV and V are not significant.

Figure 8 shows the survival curves in the different stages of the TNM post surgical histopathological stage grouping.[4] Again the prognosis becomes progressively worse from stage I to stage IV ($p=0\cdot0001$), whereas the differences between stages II and IIIA and between stages IV and V are not significant.

Comparison of the prognostic value of the different staging systems. Using the system of Evans *et al*[1] [6] as reference stage for each patient, the distribution of the patients on the stages in the other systems is shown in the Table, which also gives the number of survivors in the individual stages.

Age at diagnosis and treatment have a significant prognostic value in this population ($p<0\cdot001$). Adjusting for these factors, the survival probability in each staging system was estimated using the logistic regression model. Each staging system was found to be significant ($p<0\cdot0001$ in all cases), except the system of Thurman and Donaldson,[16] where children aged under 1 year are excluded. In this case age at diagnosis was not significant. Otherwise age at diagnosis has independent prognostic value even when the staging systems are added ($p<0\cdot001$). Thereafter all staging systems were added to the model in a stepwise manner if there was no redundancy, and the system of Evans *et al*[1] [6] was found to have independent prognostic value ($p<0\cdot0001$), whereas the other staging systems provided no further information. The significance level was set at 0·05.

It is of interest that this study confirms the existence of stage IV-S of Evans *et al*[1] [15] with a favourable prognosis among infants with metastatic disease in liver and skin. Only the systems of Sandstedt *et al*[7] and Cohen[8] give the same information.

Furthermore, it should be mentioned that the three survivors in stage IV of Evans *et al*[1] had involvement of bone or bone marrow, and a prognostic favourable subgroup of stage IV-N with involvement of lymph nodes only[16] could thus not be identified in this population.

Evaluation of the role of surgical excision of the primary tumour on the prognosis. All patients in stage I of Evans *et al*[1] [6] had the primary tumour excised. Seventeen patients had a pT1 operation

Table *Comparison of the different staging systems proposed for neuroblastomas. Values given are stages of each system and survivors/total*

Evans et al *Stage*	*Evans* et al[1,6]	*Pinkel* et al[2,3]	*Sandstedt* et al[7]	*Cohen*[8]	*James*[9]	*Thurman and Donaldson*[10]	*TNM clinical stages*[4]	*TNM post surgical stages*[4]
I	I 16/20	I 13/17 IIA 3/3	A 16/20	5 16/20	I 16/20	I 10/10 II 1/1	I 5/8 II 8/9 III 3/3	I 13/17 IIIA 3/3
II	II 30/49	I 5/9 IIA 14/21 IIB 11/19	B 30/49	5 13/20 4 17/29	I 20/32 II 10/17	I 5/9 II 10/21	I 10/14 II 9/16 III 11/19	I 1/1 II 4/8 IIIA 14/21 IIIB 11/19
III	III 2/35	IIA 1/7 IIB 0/9 IIIA 1/19	B 2/35	5 0/3 4 2/32	I 1/10 II 1/25	II 1/31	II 2/3 III 0/32	IIIA 1/7 IIIB 1/28
IV	IV 1/139	IIIA 0/36 IIIB 1/25 IIIC 2/78	C 3/139	4 0/36 1 3/103	III 0/36 IV 3/103	III 0/48 IV 1/69	IV 2/132 V 1/7	IV 2/132 V 1/7
IV-S	IV-S 4/10	IIIA 4/10	IV-S 4/10	2 2/7 3 2/3	III 4/10	III 1/1	IV 4/10	IV 4/10

performed, of whom four died: one for surgical reasons, one as a result of fatal complications due to chemotherapy, one by homocide, and one (whose tumour was a sacrococcygeal teratoma with areas of neuroblastic tissue among many other types of mature and immature structures) from progressive disease. Three patients had a pT3a operation performed and none died.

In stage II of Evans *et al*[1,6] 35 children had the primary tumour excised, by either primary (34 cases) or secondary operations (one case who had a ypT1 operation performed. Histological examination of the tumour at that time, however, revealed only mature ganglioneuroma tissue. The child, who has survived, seems thus not to have had a beneficial effect from surgery.). Of the 34 children who had the tumour excised, 21 survived (survival rate 62%) compared with nine of the 15 patients who did not have the tumour excised (including the above mentioned patients who had the secondary operation performed) (survival rate 60 %). This was not significant. Nine patients had a pT1 operation performed, five of whom survived. Twenty one patients had a pT3a operation performed, of whom 14 survived. Four patients had a pT3b operation performed, two of whom survived. There were no differences in survival between the different types of operation performed.

In stage III of Evans *et al*[1,6] 16 children had the primary tumour excised, by either primary (11 cases) or secondary (five) operations, of whom two survived (survival rate 13%), compared with none of the 19 children who did not have the tumour excised (not significant). The excisions performed were ypT1 in one case (who died), pT3a in seven (one survivor), ypT3a in one (who died) pT3b in four (no survivors), and ypT3b in three (one survivor). Thus there were no differences in survival between the different types of operation performed.

In stage IV of Evans *et al*[1,6] 28 children had the primary tumour excised, by either primary (20 cases) or secondary (8) operations, of whom two survived (survival rate 7 %), compared with one of the 111 children who did not have the primary tumour excised (survival rate 1 %) (not significant). The excisions performed were pT1 in three cases (no survivors), pT3a in four (no survivors), ypT3a in one (who survived), pT3b in 13 cases (no survivors), and ypT3b in seven (one survivor). Again there were no differences in survival between the different types of operation performed.

In stage IV-S of Evans *et al*[1] none of the children had the primary tumour excised at diagnosis, but two children had a secondary operation performed later. The operations performed were ypT0 (as the primary tumour had disappeared) and ypT1, respectively. Both of these children survived, but it is difficult to evaluate the role of surgery in the survival in these cases. Two of the other eight children with stage IV-S disease had survived also.

Discussion

All the staging systems examined here have prognostic significance for survival when based on a retrospective assignment of the extent of the disease in 253 patients. This finding is not surprising as the systems proposed by the different authors have been based on clinical experience with neuroblastomas. Only the systems of Evans *et al*[1,6] and Pinkel *et al*,[2 3] however, have been evaluated prospectively[6 15 17 3 18] and have proved their validity in predicting the prognosis for survival for the patients in the different staging groups.

For staging purposes investigations not performed have been considered negative in this study. This means that the stage of the disease in the individual patient is the minimum stage. Although radiographic skeletal surveys were only performed in 179 patients, bone marrow aspirates were only performed in 126, and regional lymph nodes were not sampled systematically and when sampled included lymph nodes adjacent to the tumour.[18] Only the following unperformed investigations may give rise to bias in the distribution of patients between the various stages: Evans' stage I: bone marrow aspirates not done in eight patients, all of whom survived, with only two receiving chemotherapy; Evans' stage II: regional lymph node biopsy examination not performed in eight patients, and bone marrow aspirates not done in 22, of whom 13 survived, with only two receiving chemotherapy (survival rate 13/22 compared with 17/27 who had bone marrow aspirates performed); Evans' stage III. regional lymph node biopsy examination not performed in six patients, and bone marrow aspirates not performed in eight, of whom one who received chemotherapy survived (survival rate 1/8 compared with 1/27 who had bone marrow aspirates performed). In patients with Evans' stages IV and IV-S disease investigations not performed could not have altered the stage.

Ideally, age should not be an independent prognostic factor in a staging system. We found, however, that age has independent prognostic significance in all staging systems except that of Thurman and Donaldson,[10] which excludes all children aged under 1 year. This is in accordance with the findings of most other authors.[1-3 6 7 14 16 19 20]

All staging systems investigated except the TNM clinical stage grouping[4] are based on non-invasive diagnostic methods as well as surgical estimation of the extent of the primary tumour. In the systems proposed by James,[9] Thurman and Donaldson,[10] and Pinkel *et al*,[2 3] and the TNM post surgical histopathological stage grouping system[4] the resectability of the primary tumour in localised and regional disease is part of the systems, whereas the resectability of the tumour is not a part of the staging systems of Evans *et al*,[1 6] Sandstedt *et al*,[7] or Cohen.[8] The latter authors note only the extent of the disease without reference to resectability. In the systems of Pinkel *et al*[2 3] and the TNM post surgical histopathological stage grouping[4] even a microscopic evaluation of lymph nodes and the margin of resection in the tumour is included. Based on this surgicopathologic staging system, Hayes *et al* found that involvement of lymph nodes in localised and regional disease was a poor prognostic feature,[18] in accordance with Ninane *et al*[21] but contrary to the findings of others.[6 19] In a retrospective analysis Tourneau *et al* found involvement of regional lymph nodes did not worsen the prognosis if the involved nodes were completely resected,[20] perhaps because all of their patients with positive lymph nodes had subsequent chemotherapy.

Based on this retrospectively staged patient population we found the staging system of Evans *et al*[1 6] superior to the other proposed systems tested for in predicting the final outcome for the children. The TNM clinical stage grouping system[4] in particular seems to be too rough in predicting the prognosis for the children with local and regional disease, as the extent of the tumour is not visualised by operation. The superiority of the system proposed by Evans *et al*[1 6] may be due to two factors. Firstly, the determination of crossing or not crossing the midline relates the tumour size to the size of the patient, whereas the measurement of the tumour mass in centimetres did not adjust tumour size for the size of the patient and it is probably the relative tumour bulk that reflects the possibility of micrometastases beside the detectable extent of the tumour. Secondly, the data collected here strongly suggest that factors other than the resectability of the tumour and the completeness of this resection have considerable influence on the prognosis, a finding which to some extent is in accordance with the findings of other authors.[1 7 14 16 19 22]

Several authors have suggested the primary role of surgical excision of the tumour for survival.[2 7 18-20 22 23] The resectability of the tumour is, however, closely correlated to tumour stage. Thus in stage I of Evans *et al*[1] all the tumours were resected, in stage II most tumours were resected, and in stage III only about half of the tumours were resected. In stage IV it seems that the sensitivity of the tumour to irradiation and chemotherapy has the major influence on survival as a 'second look' operation is carried out on those who respond to the other treatment given[17 20 24] and as resection of the primary tumour at diagnosis did not seem to influence the final outcome.[17 20] The survival rate for the children in stage III-IV who underwent a 'second look' operation was 3/13 in this study, a figure that did not differ significantly from the survival rate of 7/10 reported by Grosfeld *et al.*[24]

Conclusion

In an unselected patient population the staging system proposed by Evans *et al*[1] was found to be superior to other systems, including the recently proposed TNM system.[4] This seems to be due to the fact that factors other than the resectability of the tumour play a major role in survival. Another reason could be that the tumour size in the system of Evans *et al*[1] is related to the size of the patient, whereas the TNM clinical stage grouping system[4] did not adjust tumour size to the size of the patient.

The result is based, however, on a retrospectively staged patient population, and only a prospective investigation could clarify which staging system is best. In a prospective investigation of the ability of the TNM staging system to predict the final outcome for patients with neuroblastoma, however, the patients should be staged according to the system of Evans *et al*[1] [6] as well.

We thank the chief physicians at almost all Danish hospitals for placing hospital records at our disposal, with special thanks to the many secretaries who located them in hospital archives.

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Combined deficiency of iron and vitamin D in Asian toddlers

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SUMMARY One hundred and forty five Asian children born at Sorrento Maternity Hospital, Birmingham, were reviewed at the age of 22 months. A significant association of iron deficiency and poor vitamin D state was found. Two fifths of the children were anaemic, two fifths had a low plasma concentration of vitamin D, and one fifth had both features. This was more than simple overlap of the two deficiencies; the children with low plasma vitamin D concentrations had significantly lower concentrations of haemoglobin and serum iron. On the other hand, the deficiencies were not merely individual features of generally poor nutrition; growth and other measures of protein energy nutrition were slightly better in these children, and their plasma zinc concentration was no lower than in the children without deficiencies. It seems, therefore, that child health surveillance as currently practised—for example, growth monitoring, clinical signs, etc—will not detect these problems unless a haemoglobin determination is included. In view of the association of poor iron and vitamin D state combined prophylaxis is desirable. At present, strategies for preventing rickets in this country are not combined with attempts to detect or prevent iron deficiency. In our opinion they should be and the options are discussed.

Many aspects of infant feeding have improved since the publication of *Present Day Practice in Infant Feeding* in 1974,[1] but there are still some areas of concern, and one of these, voiced in the subsequent report in 1980,[2] is the problem of weaning in Asian infants.

It had been our impression in hospital practice that anaemia is common in Asian children during the second year of life, similar to findings in Glasgow.[3] The higher prevalence of rickets in this group is well known. As part of the follow up of Asian babies born at this hospital we took the opportunity to establish the prevalence of anaemia and vitamin D deficiency in this high risk group, to determine the causes of the individual and combined problems, and to assess the effects of these problems on the health of the children.

Patients and methods

The children studied were born at Sorrento Maternity Hospital, Birmingham. Their mothers had taken part in a study of nutritional supplementation during pregnancy,[4] and they are the same children described in our study of tuberculin response after bacille Calmette-Guérin vaccine at birth,[5] apart from four whose mothers declined the invitation for a blood test.

Altogether, 145 children aged 21–23 months were seen by one of us (HG), with the help of a health visitor and interpreter, at one of four child health centres in central Birmingham. One child was found to have coeliac disease and was not included in the study. The following assessments were made.

(a) Dietary history, including duration of time breast fed; age at introduction of cow's milk, solids, and household foods; and whether or not the child was taking vitamin supplements. A rough estimate of the amount of iron in their diet was assessed by allotting a score of 0–4 for iron content of a food whenever it had been eaten in the past four days—that is, 4 for meat, 2 for each vegetable, 1 for cereals.

(b) Psychomotor development, using the Sheridan developmental sequences.[6]

(c) Anthropometry, including weight in napkin and vest, supine length on a Stadiometer (both expressed as a standard deviation score of the American centre for health statistics),[7] and subscapular and triceps skinfold thicknesses, using Harpenden calipers.

(d) Clinical examination.

(e) Haematological investigations, including haemoglobin concentration, red cell indices, white cell count, haemoglobin electrophoresis, serum iron concentration (colourimetric method using ferrozine (Sigma Chemical Company)) and transferrin (radial immunodiffusion) and ferritin (enzyme immunoassay (Abbott Laboratories)) activities. Four children with β thalassaemia trait and 25 others had a haemoglobin concentration less than 10 g/dl and were recalled to a clinic at the hospital. Of these, 24 (four with the trait and 20 others) reattended, and further investigations included repeat blood counts in all children and blood lead concentrations and serum and red cell folate in 16.

(f) Biochemical measurements of nutritional state, including serum alkaline phosphatase and alkaline ribonuclease activities and zinc and albumin concentrations. Plasma vitamin D (25-hydroxycholecalciferol) was measured in 124 children, 59 boys and 65 girls (competitive protein binding assay based on the method of Preece *et al*[8]). As concentrations of plasma vitamin D vary throughout the year, perhaps as much as twofold, it is difficult to set one concentration below which vitamin D state is considered deficient. For this study a vitamin D concentration <10 ng/ml was taken to be suboptimal and <5 ng/ml deficient. Measurements of serum albumin and calcium concentrations were available on the mothers in pregnancy at 28, 33, and 38 weeks' gestation.

The social and ethnic background of the families had previously been documented during the pregnancy. This included religion (Muslim, Sikh, or Hindu); maternal age and educational class (grade 0: never attended school; grade 1: primary education; grade 2: 6–10 years' secondary education; up to grade 7: British university degree); duration in England; number of occupants in each room; and father's social class (according to Registrar General's classification).

Children with haemoglobin <10 g/dl were given oral treatment with iron (3 mg elemental iron/kg/day as ferrous sulphate) and those who continued follow up were seen at monthly intervals. Treatment was continued for one month after correction of their haemoglobin concentration and mean corpuscular volume. Children who failed to attend were notified to their health visitors and through them to their general practitioners.

Results

Haematological state at age 22 months. (Table 1) Ten children had β or α thalassaemia trait, and one child had coeliac disease (see Methods). Table 1 shows the haematological characteristics of the other 134 children. Anaemia and iron deficiency were common; a fifth of children had a haemoglobin concentration <10 g/dl. Commonly accepted indices of iron deficiency—for example, microcytosis, low ferritin activity, and low transferrin saturation—were found in more than half of the children.

Table 1 *Haematological characteristics of Asian children aged 22 months (excluding those with thalassaemia trait)*

	No investigated	*Mean (SD)*	*Abnormal*	
			Criterion of abnormality	*No (%)*
All children				
Haemoglobin (g/dl)	134	11·3 (1·4)	<11* <10	55 (31) 25 (19)
Serum iron (μmol/l)	124	14·9 (6·8)	<9*	15 (12)
Transferrin saturation (%)	123	15·1 (8·2)	<15*	71 (58)
Mean corpuscular volume (fl)	133	67·6 (8·7)	<70†	68 (51)
Mean corpuscular haemoglobin (pg)	133	22·2 (3·7)	<24‡	77 (58)
Plasma ferritin (ng/ml)	90	7·4 (7·2)	<7§	51 (57)
Children with haemoglobin <10 g/dl				
Serum iron (μmol/l)	20	12·7 (5·4)	<9*	3 (15)
Transferrin saturation (%)	20	10·7 (4·3)	<15*	15 (75)
Mean corpuscular volume (fl)	20	55·9 (6·6)	<70†	19 (95)
Mean corpuscular haemoglobin (pg)	20	17·2 (2·2)	<24‡	20 (100)
Plasma ferritin (ng/ml)	20	3·7 (7·8)	<7§	18 (90)
Blood lead (μg/dl)	16	17·5 (8·3)	>35‖	0
Red blood cell folate (ng/ml)	16	427 (162)	<100*	0
Serum folate (ng/ml)	16	10·4 (3·2)	<3*	0

*World Health Organisation.[9]
†Dallman.[10]
‡Nathan.[11]
§Siimes.[12]
‖Department of Health and Social Security.[13]

Vitamin D state at age 22 months. (Fig. 1) Plasma vitamin D concentration in the 124 children ranged from 2·1 to 39 ng/ml with a mean (SD) of 12·7 (6·5) ng/ml. Boys had significantly higher concentrations than girls (14·3 (6·8) *v* 11·5 (6·0) ng/ml, respectively, $p<0·05$). There were 49 children (40%) with vitamin D concentrations under 10 ng/ml and seven (6%) with concentrations under 5 ng/ml.

The 92 children taking vitamin supplements had higher vitamin D concentrations than the 32 unsupplemented ones (13·1 (6·1) *v* 11·4 (7·0) ng/ml, not significant). The well described seasonal variation in vitamin D was noted in the unsupplemented group. This seasonal variation was minimal in the supplemented children, who had higher vitamin D concentrations than the unsupplemented children in winter but had no advantage in summer.

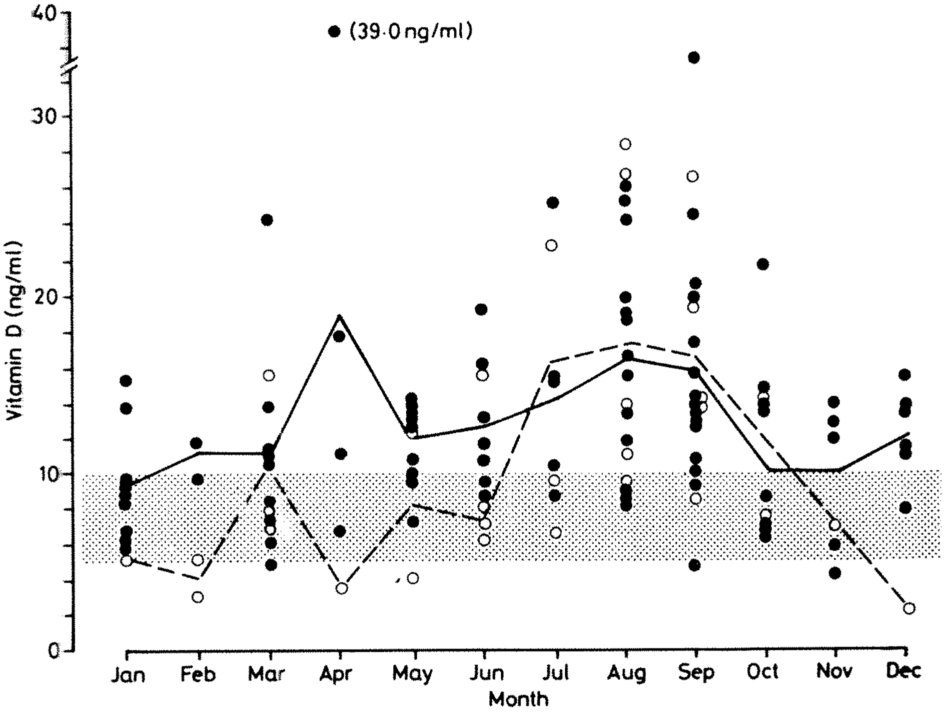

Fig. 1 *Plasma vitamin D (mean and individual values) in Asian toddlers according to seasonal variation and vitamin supplementation.* ●——● *= Vitamin supplemented children;* ○– – –○ *= unsupplemented children. Plasma vitamin D <10 ng/ml = suboptimal (shaded area), <5 ng/ml = deficient.*

Association of anaemia and poor vitamin D state. (Fig. 2) Twenty four children had both haemoglobin <11 g/dl and plasma vitamin D <10 ng/ml.

Children with plasma vitamin D <10 ng/ml had significantly lower haemoglobin and serum iron concentrations. Mean values for mean corpuscular volume, transferrin saturation, and ferritin activity were also lower but not significantly so.

Social characteristics. (Table 2) More Muslim

Table 2 *Social characteristics of Asian children at 22 months. Values are No or mean (SD)*

	Haemoglobin and vitamin D concentrations					
	Haemoglobin (g/dl)			*Vitamin D (ng/ml)*		*Haemoglobin <11 g/dl and vitamin D<10 ng/ml*
	≥11	*<11*	*<10*	*≥10*	*<10*	
Sex:						
Male	46	28	13	42	17	6
Female	37	33	16	33	32†	18††
Religion:						
Muslim	45	44†	24††	41	34	21**
Non-Muslim‡	38	17	5	34	15	3
No of years in England	5·8 (6)	4·9 (5)	4·1 (5)	5·4 (5)	4·5 (5)	3·2 (3)**
Occupants per room§	1·2 (0·5)	1·5 (0·9)*	1·4 (0·8)	1·3 (0·8)	1·3 (0·9)	1·3 (0·8)
Father's social class	3·4 (0·9)	3·7 (1)	3·9 (1)*	3·7 (0·8)	3·5 (0·9)	4·0 (1)*
Mother's educational class	2·5 (1·6)	2·1 (2)	1·6 (1·4)**	2·5 (1·7)	2·1 (1·7)	1·8 (2)
No of previous births	1·2 (1·6)	1·5 (1·7)	1·7 (2)	1·2 (1·3)	1·3 (1·5)	1·7 (1·7)

Mean significantly different from children with haemoglobin ≥ 11 g or vitamin D ≥ 10 ng/ml—*t* test: *p<0·05, **p<0·01.
Proportion of anaemic Muslim and female vitamin D deficient children greater than non-Muslims and male groups, respectively—χ^2 test: †p<0·05, ††p<0·01.
‡Prevalence of anaemia and of vitamin D deficiency was similar in Sikhs and Hindus.
§More than 1·5 occupants/room constitutes overcrowding.

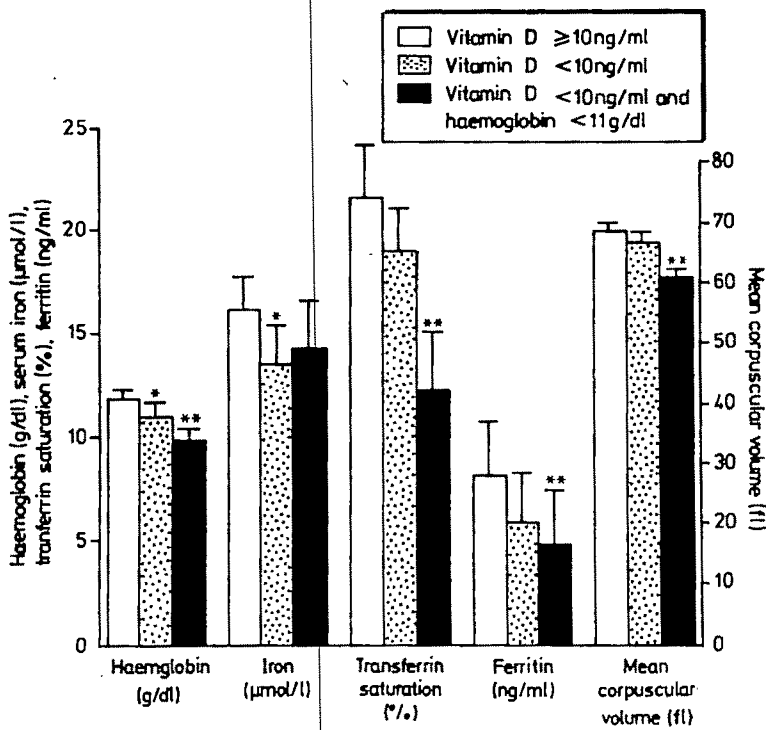

Fig. 2 *Relations between haematological characteristics and vitamin D state in Asian children aged 22 months (2SE).*
Results significantly different from children with vitamin D ≥10 ng/ml: *p<0·05, **p<0·01.

children were anaemic. The families of children with low haemoglobin and vitamin D concentrations tended to be larger and live in more crowded conditions; they had been in England for a shorter time and were of poorer social and maternal educational class, but not all of these differences achieved significance.

Nutritional characteristics. (Table 3) Both the children with anaemia and those with a low vitamin D concentration were fatter at birth and at 22 months and had lower plasma alkaline ribonuclease activity. Serum concentrations of albumin and zinc were similar in all groups.

No dietary differences were detected. Comparing

Table 3 *Nutritional characteristics of Asian children at 22 months. Values are mean (SD)*

	Haemoglobin and vitamin D concentrations					
	Haemoglobin (g/dl)			*Vitamin D (ng/ml)*		*Haemoglobin <11 g/dl and vitamin D <10 ng/ml*
	≥11	*<11*	*<10*	*≥10*	*<10*	
Birth:						
Weight (kg)	3·07 (0·5)	3·15 (0·4)	3·14 (0·6)	3·03 (0·4)	3·15 (0·4)	3·12 (0·4)
Subscapular skinfold thickness at birth (mm)	3·8 (0·9)	4·1 (1)*	4·2 (1)*	4·3 (0·5)	4·5 (1·1)	4·4 (0·8)**
At 22 months:						
Weight standard deviation score	+0·1 (0·2)	+0·3 (0·9)	+0·1 (0·7)	+0·05 (1·0)	+0·2 (1·0)	+0·2 (0·9)
Subscapular skinfold thickness (mm)	6·3 (1·5)	6·4 (1·3)	6·5 (1·3)	6·2 (1·7)	6·9 (1·4)	7·0 (1·1)*
Alkaline ribonuclease (µ/l)	520 (80)	509 (92)	513 (97)	539 (72)	494 (78)**	480 (73)*
Albumin (g/l)	43 (4)	43 (3)	43 (4)	44 (3)	44 (2)	44 (3)
Zinc (µmol/l)	10·0 (2·1)	9·7 (1·3)	10·2 (1·3)	9·8 (1·4)	10·1 (1·5)	10·2 (1·5)

Mean significantly different from children with haemoglobin ≥ 11 g or vitamin D ≥10 ng/ml—*t* test: *p<0·05, **p<0·01.

the groups with and without anaemia, there were no significant differences in mean duration of breast feeding (7 *v* 6·4 weeks), age of introduction of pasteurised cow's milk (27 *v* 31 weeks), age of introduction of solid foods (25 *v* 23 weeks), and iron score of diet in previous four days (45 *v* 44).

Psychomotor development at 22 months. Children with haemoglobin <11 g/dl showed slight but consistent delay in psychomotor development compared with the children without anaemia. The differences reached significance for fine motor and social development (haemoglobin <11 g *v* haemoglobin >11 g (mean (SD)) (months): fine motor 20·6 (1·6) *v* 21·5 (1·5), $p<0{\cdot}05$; social 20·6 (1·6) *v* 21·4 (1·4), $p<0{\cdot}01$). These differences were not observed when children with adequate and low vitamin D concentrations were compared.

Discussion

Anaemia and poor vitamin D state occurred commonly in these Asian toddlers. Two fifths had low vitamin D, two fifths were anaemic, and one fifth had both features. This study was not planned as a random sample of the local population of Asian toddlers. The sample consisted only of children born at Sorrento Maternity Hospital whose parents were sufficiently motivated to bring them to child health clinics for follow up. We suspect that some children who did not attend the clinic had less motivated parents and were more liable to be anaemic or vitamin D deficient. What was the cause and effects of these problems and what, if anything, should be done about them?

Causes.

Anaemia

Investigations suggested iron deficiency as the cause of the anaemia (low mean corpuscular volume, transferrin saturation, and ferritin activity). We consider this to be dietary in origin. Nevertheless, we could detect no dietary differences between the groups with and without anaemia. This probably reflects the crude methods used for dietary assessment, but both groups had diets suggesting a low iron intake—that is, early introduction of pasteurised milk, fairly late introduction of weaning foods, and infrequent consumption of iron containing foods. Hookworm ova were not sought, but all children were born in this country and no hookworm ova were found in Asians in Glasgow.[14] Many of the children lived in poor inner urban housing where lead poisoning may have been expected, though only one child had a high bood lead concentration. It was the custom in many households to simmer vegetables for long periods, but no cases of folate deficiency were found. Anaemia was more common in Muslims, yet they are meat eaters.

Vitamin D deficiency

Sunlight was found to be more important than diet in maintaining vitamin D concentrations in white children in neighbouring Dudley.[15] The rise in vitamin D during the summer months in our study, however, was modest and much below that seen in both Dudley[15] and Edinburgh.[16] Recorded use of dietary vitamin supplements had almost as much effect as the season in our study. It seems that for these children dietary supplementation can be almost as useful as our summer.

Association of the two deficiencies

There was a significant association, not a mere overlap, of the two deficiencies. Children with a low vitamin D concentration had lower haemoglobin and serum iron concentrations. This was particularly noticeable in winter when half of those with low vitamin D concentration were anaemic compared with none of those with an adequate vitamin D concentration. Both deficiencies were associated with evidence of an underprivileged environment—more crowded living conditions and poorer social class and maternal education. This association of the two deficiencies is not, however, just a sign of a generally poor nutritional state. The deficient children had no evidence of protein energy or zinc malnutrition. Indeed, their protein energy state was slightly better than the sufficient children in that they were a little fatter and had lower plasma activities of alkaline ribonuclease.

Effects. There was no evidence that the children with anaemia or those with poor vitamin D state suffered more ill health, nor was their growth compromised.

Psychomotor development was significantly delayed in the children with anaemia. These observations were all made by the same observer (HG) before the haemoglobin values were known, so we do not consider there is any possibility of bias. The investigation was not designed, however, to study this problem nor did the psychomotor assessments have the rigour of one of the formal measurements (such as the Denver or Griffiths scales). We therefore draw no conclusions from this but are planning an intervention study.

Detection and prevention. Clearly, monitoring of growth and other simple methods of child health surveillance would not detect these children; a haemoglobin determination is necessary.

If these continuing deficiencies of iron and vitamin D are to be prevented would dietary advice alone be enough? A substantial proportion of the iron and vitamin D intake of white English toddlers comes from fortified foods and supplements,[17] so we suspect that some reliance on fortification or supplementation, or both, will be necessary. This study suggests that a combined approach to prophylaxis against iron and vitamin D deficiency should be considered. There are three possible combined strategies.

(a) The use of an infant formula or follow up milk containing iron and vitamin D. This would have to continue throughout early childhood as these children were 22 months old.

(b) The addition of iron to Department of Health and Social Security vitamin drops. Commercial equivalents are available, but the relative availability of the iron and continued potency of vitamin D would need further assessment. Even if this was adopted, our vitamin D results suggest that reliance on regular small supplements, particularly in girls, is not effective, despite the efforts of the Asian rickets prevention campaign. This is probably because of underexposure to sunlight. In our study, however, this supplementation had as much effect as the season. In the short term it might be easier to ensure vitamin D supplementation than alter patterns of behaviour.

(c) Some years ago the fortification of baby cereals with both iron and vitamin D was a method of combined prophylaxis, but vitamin D was then considerably reduced after the epidemic of hypercalcaemia. Should this be reviewed? Opinion varies on the value of iron fortification of cereals. While the American Academy of Pediatrics commends the use of iron fortified cereal for prophylaxis[18] the European Society of Pediatric Gastroenterology and Nutrition comments that 'the addition of iron to cereals is not a reliable method of enriching the diet with iron'.[19]

These possible strategies need to be assessed and compared. In the meantime, however, we suspect that option (a)—that is, the continued use of an infant formula or a follow up milk—is likely to be the most effective, and this is what we advise individual mothers. There is evidence of good iron absorption from iron and vitamin C fortified infant formulas. Vitamin D concentrations and plasma ferritin activities are rarely low in infants receiving such formulas.[20 21]

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Treatment with iron increases weight gain and psychomotor development

M A AUKETT, Y A PARKS, P H SCOTT, AND B A WHARTON

Sorrento Maternity Hospital, Birmingham

SUMMARY Previous work at this hospital and elsewhere has shown that anaemia in toddlers is common and is associated with psychomotor delay. It seemed unclear, however, whether this association was cause and effect or merely due to the same underprivileged environment. A double blind randomised intervention study was, therefore, performed. After an initial assessment 97 children with anaemia (haemoglobin 8–11 g/dl) aged 17–19 months received either iron and vitamin C or vitamin C only (control group) for two months and were then reassessed. The children who received the iron had an increased rate of weight gain and more of them achieved the expected rate of development. While iron deficiency anaemia is unlikely to be the only factor in the slower development of children living in underprivileged circumstances, it can at least be easily identified and treated. Routine child health surveillance in such areas should include a haemoglobin determination.

The impact of protein energy malnutrition on intellectual development in developing countries has been extensively investigated.[1] In the developed world protein energy malnutrition is uncommon but iron deficiency is widespread.[2]

The relation between anaemia and cognitive development has been studied. Work in animals suggested that iron deficiency anaemia may adversely affect cognitive development and behaviour,[3] and studies in adults,[4] older children, and young adolescents[5] also showed an effect on behaviour and performance. Recent interest has been in preschool children. In 1973 a study of 230 children aged 4–5 years in New Orleans found that anaemia was associated with lower scores on testing of intelligence quotients.[6] Another study of 68 babies aged 6–24 months in Guatemala showed infants with anaemia to have substantial developmental deficits compared with their normal peers.[7] Similarly, in a group of children born in this hospital and seen again in their 'toddler' years (around 20 months) iron deficiency anaemia was very common and again was apparently associated with slower development.[8] It is not clear, however, whether the iron deficiency causes the delay or merely the two are associated evidence of an underprivileged environment.

Previous work on the use of iron supplements has yielded conflicting evidence. Some studies have shown an improvement in development using oral treatment with iron,[9] others have not.[7] Intramuscular treatment with iron may work,[10] but the suitability of giving iron in this way to toddlers can be questioned. Evaluation of these studies is difficult because of the wide age range of children included,[7 10] small sample numbers,[7 9–11] differing control groups,[9–11] and differences in the definition of iron deficiency. Also as they all used short term treatment (seven to 15 days) the differences shown may have just related to short term behaviour changes.

This study was, therefore, designed to determine the effect of psychomotor development of giving oral treatment with iron for two months to toddlers with anaemia living in an inner city underprivileged environment.

Patients and methods

Recruitment of patients. The parents of every child aged 17–19 months living in the catchment area of four child health clinics in central Birmingham were sent an invitation to attend for routine surveillance, including a haemoglobin estimation; 470 children attended. The normal clinic procedures—that is, assessment of growth and development and physical examination—were carried out as usual by the community child health service staff. In addition, capillary blood for estimation of haemoglobin was taken by one of two project nurses. Distribution of haemoglobin concentration in children attending the child health clinics is shown in Figure 1. The World Health Organisation has proposed that a haemoglobin concentration of less than 11 g/dl may be used to identify anaemia in children between the ages of 6 months and 6 years.[12] Thus 26% of the children screened were 'anaemic' using this criterion. Eight (2%) of the Asian children were severely anaemic (haemoglobin <8 g/dl). They were investigated and treated immediately. They all had simple iron deficiency anaemia. A further 25% of the Asian children and 18% of the others (almost all European) had a haemoglobin concentration between 8 and 11 g/dl, and these were recruited to the study.

Investigation and treatment plan. (Fig. 2) The children with a haemoglobin concentration of 8–11 g/dl were invited to an anaemia clinic at our hospital. Informed and written consent to the study was obtained and the patient's general practitioner informed. The following procedures were carried out.

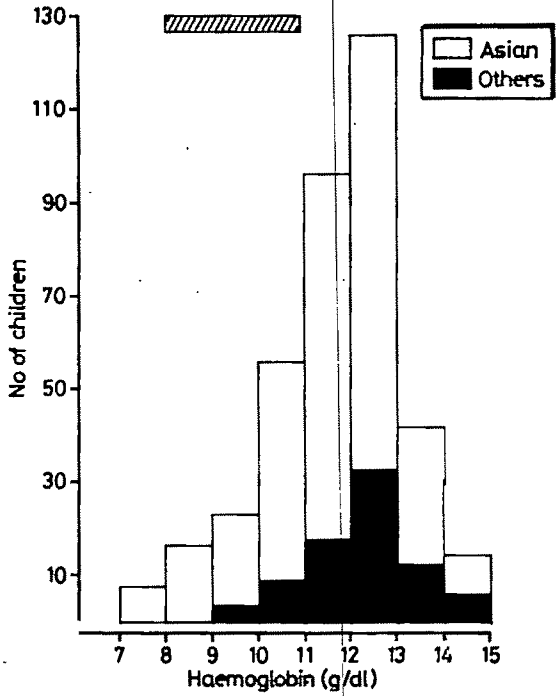


Fig.1 *Distribution of haemoglobin concentration in 470 children aged 17–19 months attending four child health clinics in inner Birmingham. Children within the hatched area were subsequently enrolled in the intervention study.*

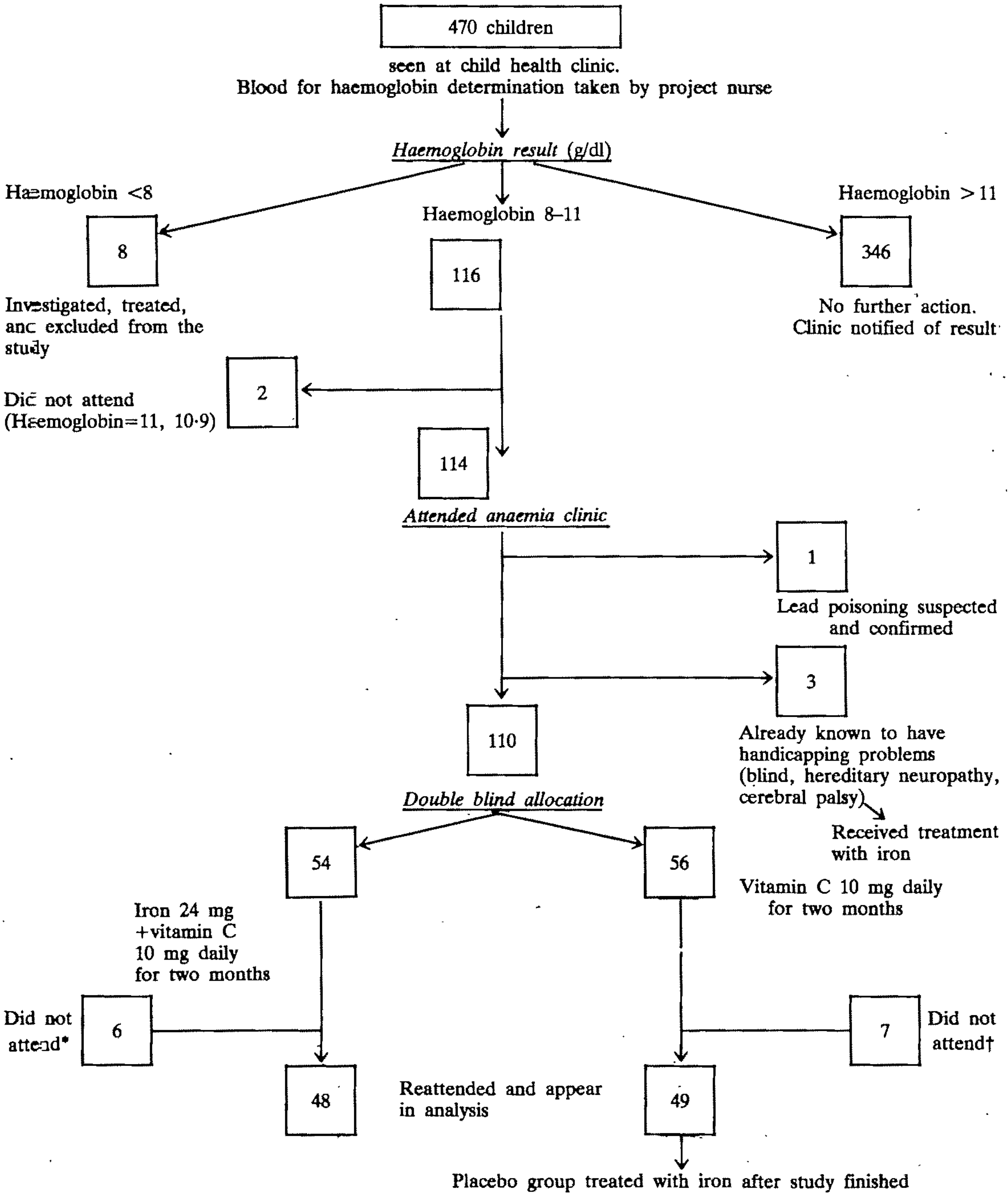
Social, family, and medical history
This was taken by the project nurses and interpreter as necessary and checked by one of us (AA or YP) using a standard form—for example, ethnic group, mother's education, housing, etc.

Growth
Growth measurements were made by the project nurses. Weight was taken with the child naked on a lever balance; length using a Harpenden Stadiometer; and head circumference by paper tape.

Haematological
One millilitre of capillary blood was taken for measurement of haemoglobin and red blood cell indices, haemoglobin electrophoresis, plasma iron concentration, which was measured colorimetrically using the Guanidine/Ferrozine method (J T Baker, Deventer, Holland),[13] transferrin, measured on a Baker Encore centrifugal analyser using anti-human transferrin (Hoecht UK Ltd, Hounslow, Middlesex) and calibrated with human transferrin (Boehringer Mannheim, West Germany), and ferritin estimation (Enzyme immunoassay, Hybritch Europe SA, Liege, Belgium).

Psychomotor development
The children were tested by one of us (AA or YP) with 24 items taken from the Denver developmental screening test[14] appropriate for the age group studied. The items were presented in the standardised manner required by the test using the standard proforma and materials.[15] The number of items that the child achieved was counted, up to a maximum possible of 24.

The age at which 25, 50, 75, and 90% of children will pass has been determined for each item.[14] Children who are average in every respect—that is, on the 50th percentile—would achieve 13 items at 18 months and 19 items at 20 months—that is, in the normal course of development they would achieve six more of the psychomotor skills tested during the two months of the study. A similar difference is seen between 19 months and 21 months—that is, six extra skills. The Denver developmental screening test was chosen as the basis for psychomotor assessment because of its suitability for the age group tested, ease of administration by a non-psychologist, good test-retest reliability, and reliability among examiners. It has been validated against the Bayley scales of infant development and the Stanford-Binet and has been standardised for use in multiracial communities.[14 16 17] As 90% of the children with anaemia were Asian and for many the first language of both mother and child was not English an interpreter attached to the project was used as an


470 children
seen at child health clinic.
Blood for haemoglobin determination taken by project nurse
Haemoglobin result (g/dl)
Haemoglobin <8
8
Investigated, treated, and excluded from the study
Haemoglobin 8–11
116
Haemoglobin >11
346
No further action. Clinic notified of result
2
Did not attend (Haemoglobin=11, 10·9)
114
Attended anaemia clinic
1
Lead poisoning suspected and confirmed
3
Already known to have handicapping problems (blind, hereditary neuropathy, cerebral palsy)
Received treatment with iron
110
Double blind allocation
54
Iron 24 mg +vitamin C 10 mg daily for two months
56
Vitamin C 10 mg daily for two months
6
Did not attend*
7
Did not attend†
48
Reattended and appear in analysis
49
Placebo group treated with iron after study finished

*One moved away, one refused medicine because of diarrhoea, one withdrew consent to remain in the study, and three failed to attend for second assessment despite chasing.

†Five moved out of Birmingham, one received iron medication from elsewhere, and one failed to attend for second assessment despite chasing.

Characteristics of these two groups were similar to each other and to the group who reattended.

Fig. 2 *Investigation and treatment protocol of the study.*

aid to the examiners in all developmental assessments.

Treatment

The children with anaemia then received either iron 24 mg (as ferrous sulphate) plus vitamin C 10 mg daily or vitamin C 10 mg alone daily. Allocation was double blind using consecutively numbered bottles (the code was only known to the hospital pharmacist). Both supplements were in the form of a palatable mixture, which looked identical. One month's supply was given at the anaemia clinic. The project nurses visited every child at two weekly intervals to encourage compliance and to take a further supply of the supplement at the end of one month.

After two months (eight to nine weeks) the children reattended and were reassessed as above. No result of any investigation from the first anaemia clinic was available until after the two month assessment was completed. A number of children in both groups had to be 'chased' to reattend for the second appointment; 15 of the treated and 17 of the placebo group were seen after the two month period (mean 75 and 76 days, respectively). As far as we are aware the only variable in the way the children were handled was whether the supplement given contained iron or not, and this variation was double blind.

Patients studied. (Table 1) The social and anthropometric details of the two groups of children who completed the intervention trial were similar, although despite randomisation the mean age of the treated group was 0·5 months below the untreated group (mean (SD): 17·9 (0·7) months *v* 18·4 (0·8) months, p<0·01). On average the children were slightly lighter and shorter than the United States reference standard.[18]

Table 1 *Characteristics of the 98 children entered in the study (Mean (SD))*

Feature	*Group*	
	Iron plus vitamin C	*Vitamin C only*
Social factors		
No	48	49
Sex (M:F)	27:21	29:20
Ethnic group:		
Asian	42	43
European	2	4
African	2	2
Other	1	0
Maternal age	27·3 (5·9)	27·2 (4·9)
No of sibs	2·4 (2·1)	2·4 (1·5)
Years in United Kingdom:		
All	9·4 (7·8)	10·5 (7·6)
Asians only	7·5 (5·3)	8·5 (5·4)
Grade of educational class:*		
0	0:25	0:19
1	1:7	1:3
2	2:13	2:15
3	3:2	3:5
4	4:1	4:3
5	5:0	5:4
Occupants per room†	1·3 (0·5)	1·3 (0·4)
Important birth history‡	3	2
Important previous medical history§	7	6
Age at first test (months)	17·9 (0·7)	18·4 (0·8)
Anthropometry at first visit		
Height	81·2 (2·6)	82·0 (3·2)
Weight	11·0 (1·4)	10·9 (1·3)
Head circumference (cm)	47·4 (1·4)	47·2 (1·8)
Standard deviation score:‖		
Weight	−0·14 (1·24)	−0·28 (0·98)
Height	−0·14 (0·87)	+0·02 (0·87)
Weight for height	−0·02 (1·41)	−0·27 (1·10)

*Grades: 0=no education; 1=1–5 years primary education; 2=6–11 years, including secondary education; 3=sixth form; 4=vocational training; 5=college.
†>1·5=Overcrowded.
‡For example, caesarean section for breech in special care baby unit for two days, preterm.
§For example, dextrocardia and chest infection, giardiasis, detached retina, diarrhoea, and vomiting.
‖Using NICHS standards.[18]

Analysis of results. The measurement of outcome—that is, improvement in haematology and weight velocity and extra skills achieved—were for the purpose of analysis firstly regarded as continuous variables, which were compared in the groups using the *t* test for significance. Then the number of children achieving various indices of normality were examined—for example, haemoglobin ±11 g/dl, weight gain ±7 g/dl, and extra skills learned ±6—using the χ^2 test with Yates's correction for significance. For each of these measurements of outcome the results were analysed as a 'pragmatic' clinical trial[19]—that is, one designed to determine whether an iron supplement *offered* to toddlers with anaemia enhanced the acquisition of psychomotor skills. For this purpose the children who completed the assessment protocol were divided into two treatment groups—those offered iron and those offered placebo—and the results compared. The results were also analysed as an 'explanatory' clinical trial[19] to test the hypothesis, 'Does a significant rise in haemoglobin (as indicated by a rise of at least 2 g/dl) enhance the acquisition of psychomotor skills in children with anaemia?' For this purpose, the children who completed the protocol were divided into two haemoglobin groups—those in whom the haemoglobin concentration rose by at least 2 g/dl and those in whom it did not—and the results compared.

Results

Effect of treatment on haematological measurements. (Table 2) As was expected the haemoglobin

Table 2 *Haematological values before and after treatment (Mean (SD))*

	Group			
	Iron plus vitamin C (n=48)		*Vitamin C only (n=49)*	
	Before	*After*	*Before*	*After*
Haemoglobin (g/dl)	9·9 (0·9)	12·1 (1·0)	10·1 (0·8)	10·4 (1·3)
No <11	48	6	49	33
Mean corpuscular volume (fl)	61·9 (7·1)	67·6 (6·2)	61·0 (6·7)	61·5 (7·0)
No <70	40	30	45	43
Mean corpuscular haemoglobin (pg)	19·8 (2·8)	22·4 (2·6)	19·6 (2·6)	19·7 (3·0)
No <24	44	32	46	46
Serum iron (µmol/l)	8·3 (4·3)	13·0 (7·1)	8·7 (3·9)	8·7 (3·6)
No <9	30/43	11/43	24/47	32/47
Transferrin saturation (%)	6·9 (4·8)	13·5 (9·8)	7·6 (5·9)	6·9 (5·0)
No <15	40/43	29/43	42/47	42/47
Ferritin (ng/nl)	8·7 (4·3)	12·9 (7·2)	7·7 (3·9)	7·7 (4·4)
No <7	18/43	7/42	24/47	21/47

Cut off points are the usual accepted lower limits of normal for this age group.[12 20-22]

concentration rose in the group receiving iron and the indices of iron deficiency all improved.

Effect of treatment on weight velocity. (Fig. 3) The rate of weight gain in the children who received iron was greater than in those who did not ($p<0·001$ by t test). Regarding individual results, whereas 75% of the treated group increased their weight by 7 g per day or more (the derived 50th centile), only 48% of the untreated group did so ($p<0·001$ by χ^2 test).

The rate of weight gain in the children whose haemoglobin concentration rose by at least 2 g/dl was greater than in those whose haemoglobin did not ($p\approx0·05$ by t test). Of those whose haemoglobin concentration rose by at least 2 g/dl, 72% increased their weight by 7 g or more, but so did 56% of those whose haemoglobin concentration did not rise more than 2 g/dl (not significant).

Effect of treatment on psychomotor development. (Fig. 4) Group results were analysed first. The mean increase in psychomotor skills in the children

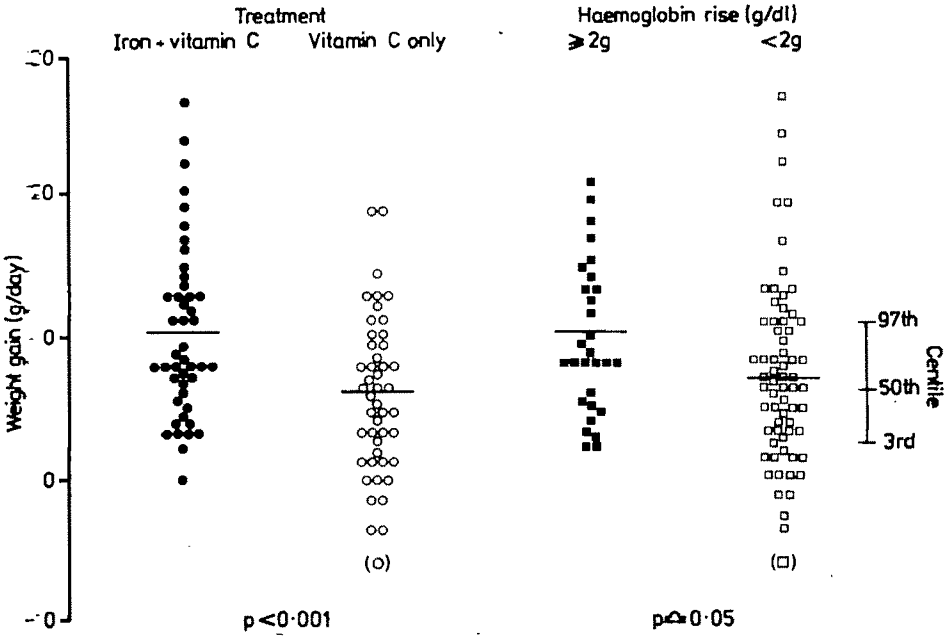


Fig 3 *Weight velocity according to treatment group and change in haemoglobin concentration. Centile numbers are based on whole year weight velocity standards for boys aged 1–5 years.*[23]

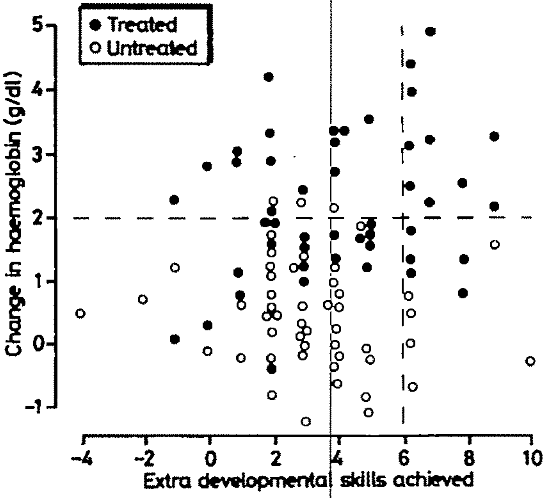


Fig. 4 *Effect of treatment on psychomotor development and haemoglobin concentration. The 'expected rate' of development (shown by vertical broken line) is based on the 50 centiles at 18 and 20 months (see text).*

who received iron was not significantly greater than in those who did not (mean (SD) increase: 4·0 (2·6) *v* 3·2 (2·3) skills) nor was it in those whose haemoglobin rose by at least 2 g/dl compared with those whose haemoglobin did not (4·3 (2·7) *v* 3·4 (2·4) skills).

Individual results were then inspected. Figure 4 shows the changes in haemoglobin concentration and the increase in number of items passed between assessments.

Overall, there was only a weak relation between the two (Spearman regression coefficient 0·18, p=0·08). Two distinct effects, however, were seen. The average child staying on the 50th centile between 18 and 20 months would acquire six more skills (see Methods). This average rate of development was achieved by 15 of the treated children (31%) but only six of the 49 (12%) in the placebo group ($p<0·05$ by χ^2 test). Alternatively, this average rate of development was achieved by 10 of the 27 (37%) children whose haemoglobin concentration rose at least 2 g/dl but only 11 out of 70 (16%) whose concentration rose by less than 2 g/dl ($p<0·05$).

Combining these two points then, 'effective treatment' could be defined as 'received treatment with iron *and* haemoglobin rose by less than 2 g/dl'. The average rate of development was achieved by 10 of the 24 (42%) effectively treated children but by only six out of 47 (13%) of those who had not received effective treatment (neither received iron nor whose haemoglobin rose by more than 2 g/dl) ($p<0·02$).

Nevertheless, it will be noted that 14 children failed to acquire six more skills even though they had received iron and their haemoglobin had risen by more than 2 g/dl.

Discussion

In this study toddlers with anaemia who received treatment with iron for two months when compared with a control group with anaemia who did not receive treatment with iron were different in two respects. They had a faster weight velocity and more of them achieved the expected increase in psychomotor skills.

Weight velocity. Weight velocity over the two month period was significantly greater in the treated group than in the control group. Increase in weight velocity during treatment with iron has been shown before both when treating toddlers with anaemia successfully[24] and when giving prophylactic iron supplements to normal boys.[25] This increase is seen in infants who are normal weight as well as those who are underweight at the time.

This finding may relate to the correction of the anorexia and listlessness reported as associated with iron deficiency anaemia in children,[26] but the effects of iron deficiency are protean.[27]

Psychomotor development. Our methods and results are compared with previous studies in Table 3. This study was based on a narrow, well defined age group and used a fairly long period of treatment with iron.

Before the study we were sceptical that iron deficiency had an independent effect on developmental delay. We suspected that the iron deficiency and poor development were merely effects of the same deprived environment, many aspects of which could contribute both to iron deficiency anaemia and to delayed development. Similar views had been expressed by Werkman *et al.*[26] This, however, does not seem to be so. This intervention study suggests that there is indeed a direct relation between iron deficiency and delayed psychomotor development.

The differences between the treated and untreated groups and the below or above 2 g/dl rise in haemoglobin groups were clearest when the 'expected' achievement of six extra skills was in effect counted as 'success' or 'failure' of intervention. We suspect this indicates a 'threshold' effect; once treatment with iron has an effect the acquisition of extra skill proceeds rapidly.

A large number (5–30%) of young children have been found to be anaemic in various surveys,[2 3 29–32] and many more may be iron deficient (21–55%).[2 29–32] Two studies have indicated that iron

Table 3 *Effect of iron on development. Comparison of this study with previous reported studies*

	This study	*Lozoff* et al[7]	*Oski and Honig*[10 28]	*Walter* et al[9]	*Oski* et al[11]
Criterion of abnormality to enter study	Haemoglobin 8–11 g/dl	Haemoglobin <10·5 g/dl	Haemoglobin <10·5 g/dl, mean corpuscular volume ≤73 u³, serum iron <50 μg, and transferrin saturation ≤12%	(a) Haemoglobin <11 g/dl and two abnormal biochemical tests (b) Haemoglobin >11 g/dl and one or more abnormal test or haemoglobin rise of >1 g/dl	Haemoglobin >11 g/dl and (a) normal mean corpuscular volume, electrophoresis, and ferritin (b) normal mean corpuscular volume and electrophoresis and low ferritin (c) normal mean corpuscular volume, high electrophoresis, and low ferritin (d) low mean corpuscular volume, high electrophoresis, and low ferritin
Age group (months)	17–19	6–24	9–26	15	9–12
Treated group					
No	48 anaemic. Iron deficiency	15 anaemic. Iron deficiency 19 non-anaemic	12 anaemic. Iron deficiency	10 anaemic. Iron deficiency 15 non-anaemic. Iron deficiency	(a) 10 normal (b) 10 iron depleted (c) 10 iron deficient (biochemically) (d) 8 iron deficient (biochemically and cellular)
Treatment/day	Oral iron 24 mg+vitamin C	Oral ferrous ascorbate 5 mg/kg plus 'carrier'	Intramuscular iron dextran complex dose dependent on degree of anaemia	Oral iron 3–4 mg/kg day	Intramuscular iron 50 mg (iron dextran)
Treatment period (days)	60	6–8	5–8	9–15	7
Control group					
No	49 also anaemic, iron deficient	13 anaemic, iron deficient. 21 non-anaemic	12 iron deficient and anaemic	12 non-anaemic, iron sufficient	10 normal as (a) above
Treatment (if any)	Vitamin C 10 mg daily	'Carrier' alone	Intramuscular sterile saline	Oral iron 3–4 mg/kg/day	Intramuscular iron 50 mg (iron dextran)
Psychomotor test	Denver	Bayley scales	Bayley scales	Bayley scales	Bayley scales
Results: treated *v* controls	31% treated children achieved six or more new skills *v* 12% in controls ($p<0·05$); 37% of those whose haemoglobin rose >2 g did so *v* 16% of those whose haemoglobin rose by <2 g ($p<0·05$); 42% effectively treated achieved six or more new skills *v* 13% in controls ($p<0·02$).	Although scores improved in all groups iron treated anaemia did not increase more than placebo treated, anaemic, or non-anaemic (treated or not) groups	Significant increase in mental development index ($p<0·05$); 66% of treated gained 10 or more points *v* 25% of controls	Mental development index improved in treated anaemic group ($p<0·05$). No change in treated controls. No change in treated non-anaemic iron deficient group	77% of treated iron deficient group increased 10 or more points *v* 20% of treated non-iron deficient group ($p<0·001$)

deficiency may affect development even before the children become anaemic (haemoglobin <11 g/dl).[9 11] Long term iron deficiency may, therefore, have major effects on learning and scholastic performance, and studies in school age children seem to support this.[5 33] There is, therefore, mounting evidence and concern[29] that iron deficiency anaemia can produce delayed development in children, and there has been some suggestion that this is not readily reversible.[34] Nevertheless, in our study there was overall only a weak relation between rise in haemoglobin concentration and improved development. Furthermore, a number of children failed to show a satisfactory improvement in development despite a definite rise in their haemoglobin concentration. So it is very unlikely that iron deficiency is the only culprit in the slower development of underprivileged children.

Implications for the child health services. While iron deficiency anaemia is not the *only* factor in the slower development of children living in underprivileged circumstances, it is one that at least can be easily identified and treated. The implications for the child health services are important. In our opinion a programme is needed to hunt out and treat iron deficiency in toddlers. The current child health services do not achieve this, although the incorporation of a haemoglobin screening test into the child health surveillance programme would not be difficult. The logistics of providing a few pennyworth of iron against those of repairing social disadvantage do not bear comparison.

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Twenty five years ago

The reproductive histories of mothers of patients suffering from congenital diplegia

T T S Ingram and Elspeth M Russell (Edinburgh)—Arch Dis Child 1961;**36**:34–41

'Two hundred mothers with children suffering from congenital diplegia were studied, 117 boys and 83 girls, and 20 were one of twins. Thier ages ranged from 13 months to 30 years, and they tended to be preselected by social class, intelligence and probably other characteristics, with an excess of patients in social classes I and II.'

This and a previous series were assessed. 'The reproductive histories of the mothers of diplegic patients in the two series were examined. The mothers were older when they married and more were over 30 years of age when they gave birth to diplegic children than expected. They had fewer conceptions than married child-bearing women in the population of Scotland and their pregnancies were more widely spread. A high proportion of their pregnancies aborted or were otherwise abnormal. Many of their offspring were stillborn, died in infancy or showed neurological or other defects if they survived. Less than half the conceptions resulted in the birth of healthy offspring who survived the first year of life. There tended to be periods of relatively decreased fertility immediately before and after the birth of patients. Pregnancies contiguous to those resulting in the birth of diplegic children were more often abnormal than those which were more remote.

'The findings support the thesis that mothers of diplegic patients may have underlying abnormalities of reproductive capacity which may be responsible for both disorders of pregnancy, labour and delivery, and for the production of abnormal offspring. The causes are obscure but maternal age may be a factor, as may chronic illness (diabetes, thyrotoxicosis and gynaecological disorders) affecting one-fifth of these mothers. Male reproductive function and mutating or recessive genes also have to be considered.'

(Dr Tom Ingram was one of the first paediatricians to devote a large part of his time and energies to research in the field of cerebral palsy. Apart from helping to develop an excellent service for children with cerebral palsy in Edinburgh he contributed much to the epidemiology, aetiology, and treatment of these children. NEIL GORDON.)

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Immature sound localisation and abnormal development

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SUMMARY This investigation tested the hypothesis that high risk infants showing immaturity in localisation of a sound stimulus would be more likely to have appreciable neurodevelopmental dysfunction. The cohort comprised 112 infants, 66 of whom were classified as 'high risk'. Every infant underwent a neurological and developmental assessment, a sound localisation response test, and an audiological examination when necessary. The first examination was performed at age 8–9 months and was repeated between six and eight months later. It was found that if the sound localisation response was mature at the first examination normal development could be anticipated at the second examination. If an immature sound localisation response was shown then considerable dysfunction could be anticipated in about half of the infants. It is suggested that special attention be paid to the maturity of the sound localisation response in infants during auditory screening procedures, and an immature response should alert the examiner to the possibility of appreciable abnormality in development.

Preterm infants often show developmental delay or dysfunction during early life. Many of these infants have normal potential and will subsequently catch up their peers. A proportion, however, remain delayed and will later manifest signs of mental retardation or cerebral palsy, or both.[1] With the advent of sophisticated, modern techniques of perinatal care, many more preterm infants are being saved, and the clinician is faced with the dilemma of diagnosing important psychomotor development problems requiring early intervention.[2] Any procedure that might aid the correct early identification of these high risk infants would therefore be of considerable value.

The sound localisation response seemed an appropriate area of investigation when a number of infants were referred to our child development centre by an audiologist with the comment that the infants' hearing was normal but that their ability to localise the source of a sound stimulus was not appropriate for their age. On developmental assessment a high proportion of these infants were found to have important neurodevelopmental dysfunction requiring intervention.

Various authors have described a developmental sequence of auditory localisation.[3 4] On this basis, a study was planned wherein a mixed sample of infants, comprising a high risk group and a low risk group, underwent a test for sound localisation response. The results were correlated with their developmental attainments at that time and six months later. It was hypothesised that those infants who showed an immature sound localising response would be more likely to have appreciable abnormal development subsequently.

Patients and methods

One hundred and twenty two infants between the ages of 8 and 9 months, attending well baby clinics, were selected by a clinic nurse (who was not participating in the study and was not aware of the developmental state of the infants). Of these, 66 were classified as high risk by virtue of having been exposed to gestational or perinatal events known to be potentially damaging to the central nervous system (Table 1). The remaining 56 infants, who had not been subjected to known risk factors, comprised the low risk group. The two groups were similar with regard to ethnic origin and socioeconomic state of the father. The examiners participating in the study were unaware of the classification of the infants.

Table 1 *Distribution of risk factors among the high risk group*

	Full term infants (n=15)	*Premature infants*	
		>1500 g (n=43)	*<1500 g (n=4)*
Fetal distress	4	2	
Meconium aspiration	2		
Asphyxia	8	7	2
Small for dates	6	8	
Respiratory distress syndrome	2	14	3
Jaundice		18	3
Apnoeic episodes		7	1
Patent ductus arteriosus		3	1
Hypoglycaemia	2	17	
Convulsion		2	
Sepsis	2	2	1

The developmental assessment of the preterm infants was corrected for gestational age. The study was divided into two stages, initial examination and follow up.

Initial examination comprised the Bayley scale of infant development,[5] including mental developmental index and psychomotor developmental index, the Stycar hearing screening test,[6] and sound localisation response test.[3] The mental and psychomotor developmental indexes provide an objective assessment of mental and psychomotor development and have a low degree of observer bias; they were reported separately to provide a more reliable profile of developmental skills.

In the hearing tests the infant was placed on the mother's lap opposite an observer. The examiner, stationed one metre from the infant and outside his range of peripheral vision, produced sound stimuli of various frequencies, at and 45° below and above ear level. The infant's response was recorded as normal if, at 8 months, he was able to look directly at the sound source below ear level or in an arc when the stimulus was above ear level.

Any infant who showed an immature sound localisation response was referred for complete audiologic evaluation, including brain evoked response audiometry.

The cohort was re-examined between six and eight months later. All babies again underwent the Bayley developmental assessment[5] as well as complete physical and neurological examination.

Any health or developmental problems occurring over this period were treated according to the routine procedure operative at the time in the clinic.

Results

Of the 122 originally recruited subjects, 112 (92%) completed the study. Of the 10 who dropped out of the study, four belonged to the high risk and six to the low risk group (Table 2). They all failed to complete the second stage of the study. The sound localisation response was normal in all 10 of these children, and their developmental quotient was similar to the cohort group.

An immature sound localisation response was shown by 12 infants, 10 (16%) of whom were from the high risk and two (4%) from the low risk group. This figure was significant only at the level of $p<0·1$ (by χ^2 analysis) but probably indicates a trend.

Significantly lower mental and psychomotor developmental indexes were found in subjects with an immature response when compared with those with a mature response. These differences were already evident at the age of 8–9 months and became more pronounced by the age of 14–15 months (Table 3).

In Tables 4 and 5 the scores of the mental and psychomotor developmental indexes of the total cohort are analysed with reference to the type of sound localisation response. Mean scores for the low risk group minus 2 standard deviations were used as the cut off point for normal developmental performance (mental and psychomotor developmental indexes <76 and <73·5, respectively). This analysis showed a significantly lower performance in the

Table 2 *Cohort tested for sound localisation response*

	Group		*Total cohort (n=122)*
	High risk (n=66)	*Low risk (n=56)*	
Sex (M:F)	37:29	33:23	70:52
Initial examination (months/days):			
Age range	7/5–10/14	7/15–10/19	
Mean age	8/21	8/21	8/21
Follow up examination (months/days):			
Age range	13/0–18/17	13/4–18/11	
Mean age	15/10	15/26	15/18
Dropouts	4	6	10
Completed study (No (%))	62 (94)	50 (89)	112 (91)
Mature:immature sound localisation response (No (%))	52:10 (16)	54:2 (4)	106:12 (11)

Table 3 *Relation between developmental quotient (mean (SD)) and maturity of sound localisation response*

Developmental index	*Sound localisation response*		*t Value*	*p Value*
	Immature	*Mature*		
At 9 months:				
Mental	84·2 (26·0)	101·7 (12·6)	3·743	<0·0005
Psychomotor	66·5 (16·9)	89·0 (14·8)	4·980	<0·0005
At 15 months:				
Mental	72·4 (20·4)	99·1 (11·8)	6·605	<0·0005
Psychomotor	68·2 (14·0)	94·1 (12·6)	6·559	<0·0005

group with an immature response. The sensitivity for the mental and psychomotor developmental indexes was 58% and 50%, respectively, while the specificity was 95% and 94%, respectively. Positive predictive value was 58% and 50% and negative predictive value 95% and 94%, respectively. Total accuracy was 90%.

Ten of the 12 infants in the group with an immature response were premature and suffered from additional risk factors. No specific combination of potentially damaging events could be implicated (Table 1). No hearing defect was found in the infants with an immature sound localisation response.

Table 6 shows that, irrespective of risk category, it was in fact the maturity of the sound localisation response that was associated with the performance on the Bayley test. Despite the difference in the score of psychomotor developmental index ($p<0{\cdot}05$) between those with a mature response in favour of the low risk group, when maturity of the sound localisation response was considered this disparity became much more significant ($p<0{\cdot}0005$).

Table 4 *Screening value of sound localisation response test for mental developmental index*

Sound localisation response	*Developmental quotient*		*Total*
	<76	*>76*	
Immature	7	5	12
Mature	5	95	100
Total	12	100	112

Sensitivity 58%; specificity 95%; positive predictive value 58%; negative predictive value 95%; total accuracy 91%; $\chi^2=26{\cdot}50$; $p<0{\cdot}0005$.

Table 5 *Screening value of sound localisation response test for psychomotor developmental index*

Sound localisation response	*Developmental quotient*		*Total*
	<73·4	*>73·4*	
Immature	6	6	12
Mature	6	94	100
Total	12	100	112

Sensitivity 50%; specificity 94%; positive predictive value 50%; negative predictive value 94%; total accuracy 89%; $\chi^2=17{\cdot}32$; $p<0{\cdot}005$.

Discussion

Auditory screening programmes in infancy are being used increasingly for the early detection of hearing defects in infants. The purpose of this study was to determine whether the incorporation of an assessment of the infant's ability to localise a sound source might provide information on his neurodevelopmental state.

In an attempt to address this question a simply performed assessment of the infant's ability to localise the origin of a sound source was evaluated by comparing the maturity of the response of his developmental performance at the time and again six to eight months later. While other studies have shown an association between an immature sound localisation response and subsequent language delay at age 36 months,[7 8] our study showed the correlation between sound localisation response and subsequent development at an earlier age.

Analysis of the validity of the sound localisation response indicated that if this was mature at the age of 8–9 months then the clinician could reliably predict normal development six months later. An immature response, however, was associated with significantly delayed mental and psychomotor developmental indexes in 58% and 56% of subjects, respectively, thus yielding a large number of false positives.

Our study group comprised 54% high risk infants. This might resemble the situation seen in neonatal special care follow up clinics, and the positive predictive value of the sound localisation response test would therefore be similar to our findings. The well baby clinic population is, however, a different one, and it might be assumed that the pretest

Table 6 *Analysis of the relation between maturity of sound localisation response, developmental quotient, and risk category. Values are mean (SD)*

Developmental index	*Sound localisation response*						
	Mature		*t Value*	*p Value*	*Immature (n=12)*	*t Value*	*p Value*
	Low risk group (n=48)	*High risk group (n=52)*					
Mental	98·9 (11·5)	98·9 (12·0)	NS	NS	70·5 (20·4)	6·46	<0·0005
Psychomotor	96·4 (11·5)	91·7 (13·7)	1·82	<0·05	68·2 (14·0)	7·27	<0·0005

NS=not significant.

likelihood of developmental delay would be ±5%. The positive predictive value would, therefore, decrease to 38% and the negative predictive value would increase to 98%. Even in this situation it is evident that the sound localisation response test would be of definite value to the clinician.

We therefore confirm that the sound localisation response can be of value in providing information on the developmental state of the infant. The procedure is easy to learn and takes no longer than three to four minutes to perform. We recommend that it be incorporated into routine infant follow up examinations as well as any screening programmes. Medical or paramedical staff should also find this developmental milestone useful in evaluating infants, especially high risk premature infants or those with questionable development, a normal sound localisation response being associated with a favourable outlook. It is to be emphasised that evaluation of the sound localisation response is not a short cut to providing a developmental diagnosis but can help in the early selection of those infants at greater risk for appreciable neurodevelopmental dysfunction.

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Low serum thyroxine concentrations and neural maturation in preterm infants

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SUMMARY The effect of hypothyroxinaemia on postnatal progression of the motor nerve conduction velocity was studied in 33 very low birthweight infants.

Serum concentrations of thyroid stimulating hormone, triiodothyronine, and thyroxine were determined at birth and at ages 3, 7, and 21 days. Nerve conduction velocity was measured in the first week of life, on day 21, and at 40 weeks' postmenstrual age.

Seven infants maintained their thyroxine concentration above 60 nmol/l (4·67 μg/100 ml) throughout the study. Three of these infants needed mechanical ventilation and one had an intraventricular haemorrhage. Twenty six infants developed hypothyroxinaemia (thyroxine <60 nmol/l). The nerve conduction velocity was delayed in 13 infants, two on day 21 and 11 at 40 weeks' postmenstrual age. The delay was equivalent to 1·9–4·4 weeks. All these infants belonged to the group with depressed thyroxine concentrations. The delay in progression in nerve conduction velocity was associated with prolonged hypothyroxinaemia, especially in those infants who also required ventilation.

Further studies are in progress to study the effect of thyroid hormone on the nerve conduction velocity in preterm infants.

Low thyroxine concentrations are well documented in preterm infants, especially those who are less mature or have respiratory distress syndrome.[1 2] A combination of low thyroxine concentrations with raised thyroid stimulating hormone concentrations has been reported in only one study and was due to a relative iodine deficiency.[3] In all other reports low thyroxine concentrations have been associated with either normal or low thyroid stimulating hormone concentrations. It has therefore been assumed that low thyroxine concentrations are an expression either of immaturity or of a disturbance of the hypothalamic-pituitary-thyroid axis.[4] Whether the disturbance is secondary to, or associated with, abnormal cerebral metabolism in association with the periventricular-intraventricular haemorrhage to which these infants are prone has so far not been documented.[5]

Low thyroxine concentrations normalise spontaneously over three to nine weeks.[6 7] No consistent physiological disturbances have been noted in these immature infants, nor is it known whether these transient low thyroxine concentrations have a similar harmful effect on the developing nervous system, as noted in children with prolonged hypothyroxinaemia due to congenital hypothyroidism. Delayed myelination has been observed in hypothyroidism, both in humans and animals.[8] Slow nerve conduction velocity and immature visual evoked potentials have been reported in infants with congenital hypothyroidism and are believed to be an expression of the decreased peripheral and central myelin formation.[9 10] If the assumption can be made that abnormal thyroid function will also affect myelination in the premature infant then one would expect to find a slower postnatal maturation of nerve conduction velocity in infants with low thyroxine concentrations compared with those with normal thyroid function.

The aim of the present study was to assess neurological maturation as measured by nerve conduction velocity in premature infants with normal and abnormal thyroid function and to find out whether there is any relation between periventricular-intraventricular haemorrhage and abnormal thyroid function.

Patients and methods

Thirty three very low birthweight infants, admitted to Hammersmith Hospital regional intensive care unit between February and September 1984, were enrolled in a longitudinal study. Informed parental consent was obtained in each case. All infants had a gestational age of 31 weeks or less and a birth weight of 1500 g or less. Gestational age was obtained from maternal dates, early prenatal ultrasound assessments when available, and clinical assessments according to the criteria of Dubowitz *et al.*[11] Infants were only included if these initial examinations agreed to within one week.

Serial measurements of triiodothyronine, thyroxine, and thyroid stimulating hormone were taken on cord blood and on venous samples on days 3, 7, and 21. Samples were also obtained in seven children at 40 weeks' postmenstrual age.

Assays. Serum triiodothyronine, thyroxine, and thyroid stimulating hormone concentrations were measured by double antibody radioimmunoassay MRC, using MRC standard 68/38 for the thyroid stimulating hormone assay. Normal ranges of thyroxine and triiodothyronine for adults are 70–150 nmol/l and 1–2·8 nmol/l, respectively. The samples were assayed in batches and the results unknown until after measurement of nerve conduction velocity had been performed at 40 weeks' postmenstrual age.

Nerve conduction velocity was calculated using combined velocities of the ulnar and posterior tibial nerves as described by Moosa and Dubowitz,[12] using a Medelec MS 8 machine. This method has been shown to be reliable and can predict gestation with a standard deviation of 1·14 weeks.[13] Nerve conduction velocity was measured in the first week of life, on day 21, and as close as possible to 40 weeks' postmenstrual age (range 39–43 weeks).

Cranial ultrasound examinations were performed daily during the first week of life to diagnose and time the occurrence of periventricular-intraventricular haemorrhage. An ATL mechanical sector scanner was used.

Statistical analysis was determined by the Fisher's exact test.

Results

The infants were divided into two groups based on the thyroxine concentrations being consistently at or above 60 nmol/l (4·67 µg/100 ml) or below 60 nmol/l at any time during the study. This concentration is often taken as a cut off point for preterm infants in neonatal screening programmes.[3]

Group 1 (thyroxine ≥60 nmol/l) consisted of seven infants and group 2 (thyroxine <60 nmol/l) of 26. Clinical findings of the two groups are summarised in the Table. The mean gestational age was 29·1 weeks (range 28–31) in group 1 and 28·6 (26–31) in group 2. The infants in group 1 seemed less severely ill. Of the seven infants in group 1, two needed mechanical ventilation for respiratory distress syndrome and one for retained lung fluid, whereas in the second group 15 of the 26 infants needed ventilatory help, 12 for respiratory distress syndrome and three for apnoeic spells of immaturity.

Thyroid function. In the seven infants who maintained the thyroxine concentration above 60 nmol/l (group 1) a relative trough was seen on day 7, with a pronounced rise on day 21. Of the 26 infants who developed hypothyroxinaemia (thyroxine <60 nmol/l) (group 2), 12 infants reached a trough on day 3 and 14 on day 7. In 18 of the 26 infants the thryoxine concentration was still below 60 nmol/l on day 21, and the mean concentration on day 21 in group 2 was still low (57 nmol/l (4·43 µg/100 ml)). In two of the seven infants, tested at 40 weeks' postmenstrual age, the thyroxine concentration was still below 70 nmol/l (5·44 µg/100 ml).

Triiodothyronine concentrations were found to be immeasurable (<0·6 nmol/l (0·04 ng/ml)) in 24 of our 33 infants during the first three days of life. Triiodothyronine concentrations were still below 0·6 nmol/l on day 7 in 17 infants. Only one infant with a triiodothyronine concentration below 0·6 nmol/l on day 7 belonged to group 1, the other 16 belonging to

Table *Clinical findings in the two study groups*

Study group	*n=*	*Gestational age (wks) (mean (range))*	*Birth weight (g) (mean (range))*	*Intermittent positive pressure ventilation*	*Periventricular-intraventricular haemorrhage*
Thyroxine ≥60 nmol/l	7	29·1 (28–31)	1035 (635–1350)	3	1
Thyroxine <60 nmol/l	26	28·6 (26–31)	1107 (770–1500)	15	15

Conversion: SI to traditional units—Thyroxine: 1 nmol/l=0·078 µg/100ml.

group 2. Although the triiodothyronine concentrations tended to rise during the study in both groups, the mean concentration in group 2 was still low on day 21 (0·85 nmol/l (0·055 ng/ml)).

Thyroid stimulating hormone concentrations remained below 20 mU/l in all infants throughout the study, but in three of these there was a raised concentration on one occasion only (on day 3, range 10·2–19·8 mU/l). All other thyroid stimulating hormone concentrations were normal (range <1–7·5 mU/l).

Nerve conduction velocity. Normal postnatal acceleration of the nerve conduction velocity was found in 20 infants, while the velocity was delayed in 13 infants. In group 1 (with normal thyroxine concentrations) the nerve conduction velocity was normal on day 21 and at 40 weeks' postmenstrual age (Fig. 1(a)).

In group 2 (with one or more low thyroxine concentrations) the nerve conduction velocity was delayed in 13 of the 26 infants at 40 weeks' postmenstrual age. Two of these infants already showed a slow velocity at 21 days, whereas the remainder were normal at that stage. The other 11 showed a normal increase between the first and the third week of life and the delay was first noted at 40 weeks' postmenstrual age (Fig. 1(b)). The incidence of delay in nerve conduction velocity at 40 weeks' postmenstrual age, of 1·9 weeks or more, was significantly different between the two groups ($p<0\cdot02$ by one tailed Fisher exact test).

Ten of the 13 infants with a delay in nerve conduction velocity had prolonged hypothyroxinaemia (low thyroxine concentrations on day 7 and 21) (Fig. 2). Nine of these 10 infants required ventilation. Eight further infants had prolonged hypothyroxinaemia but a normal nerve conduction velocity at 40 weeks' postmenstrual age, and only three of these infants were ventilated. A combination of ventilation and prolonged hypothyroxinaemia was thus present in nine of the 13 infants with a delay in nerve conduction velocity and in only three of the 13 with normal nerve conduction velocity ($p<0\cdot02$).

No difference in the nutritional state at 40 weeks'

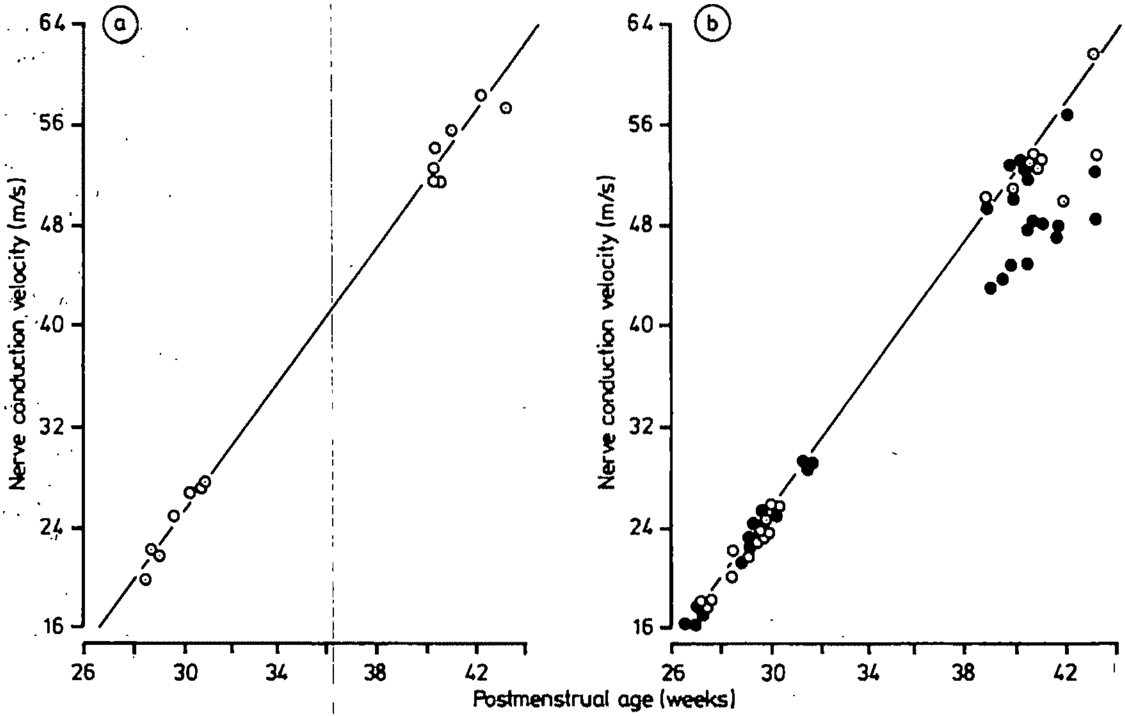

Fig. 1 *Nerve conduction velocity during the first week of life (lower cluster) and at 40 weeks' postmenstrual age (39–43 weeks) (upper cluster) in infants with (a) thyroxine ≥60 nmol/l and (b) thyroxine <60 nmol/l (○=thyroxine <60 nmol/l on one occasion (day 3 or 7); ●=thyroxine <60 nmol/l on two occasions (day 7 and 21)).*

Conversion: SI to traditional units—Thyroxine: 1 nmol/l≈0·078 µg/100ml.

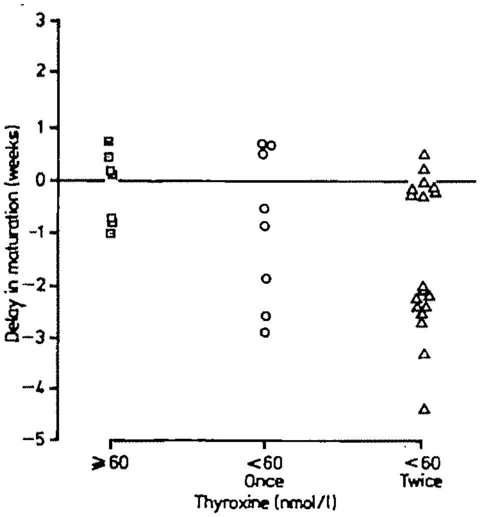

Fig. 2 *Progression in nerve conduction velocity between birth and 40 weeks' postmenstrual age in infants with a thyroxine concentration ≥60, <60 on one occasion (day 3 or 7), and <60 nmol/l on two occasions (day 7 and 21).*

Conversion: SI to traditional units—Thyroxine: 1 nmol/l≈0·078 μg/100 ml.

postmenstrual age in terms of overall weight gain could be found between infants with and without the delay in nerve conduction velocity.

Ultrasound findings. Sixteen infants developed a periventricular-intraventricular haemorrhage. A haemorrhage was noted in 15 of the 26 infants with low thyroxine concentrations compared with one of seven with normal thyroxine concentrations. ($p<0·05$).

Discussion

Our findings support previous observations that prematurity and severe illness are associated with a disturbance of the thyroid axis and thus with hypothyroxinaemia in the absence of increased thyroid stimulating hormone concentrations. Twenty six (78%) of our patients developed thyroxine concentrations below 60 nmol/l and 21 (65%) still had concentrations below 60 nmol/l at 3 weeks of age. The high incidence of hypothyroxinaemia and the slow recovery rate in this study, compared with other studies,[6] are most likely due to the immaturity of our population.

The high incidence of periventricular-intraventricular haemorrhage in the population might be another important associated factor in the hypothalamic disturbance. Fifteen of the 26 infants with low thyroxine concentrations had an associated haemorrhage compared with only one of seven with normal concentrations. It is noteworthy, however, that in six infants low thyroxine concentrations were already present before the bleed could be visualised by ultrasonography and no correlation could be found between the size of the bleed and the degree of the endocrine disturbance. It is thus possible that the hypothalamus is not directly affected by the haemorrhage itself but by the circulatory disturbance leading to it.

This study also shows that the hypothyroxinaemia may be prolonged beyond the first two to three weeks of life. This is supported by the results of Chowdry, who studied a comparable population and only found stabilisation of serum thyroxine between 7 and 9 weeks postnatally.[7] Only seven of our infants could be tested at 40 weeks' postmenstrual age, and two still had a thyroxine concentration below 70 nmol/l. Unfortunately, we were unable to document the exact duration of the hypothyroxinaemia in most of our infants as most of them were referred back to the referring hospital shortly after the end of the study.

This study also shows an association between thyroxine concentrations and nerve conduction velocity. Normal maturation was found in all infants with normal thyroxine concentrations, whereas 13 of the 26 infants with low concentrations had a delayed maturation. The nerve conduction velocity seemed to be more often delayed in those infants who still had thyroxine concentrations below 60 nmol/l on day 21. A number of infants, however, had a normal nerve conduction velocity at 40 weeks' postmenstrual age in spite of prolonged hypothyroxinaemia. While most of the infants with prolonged hypothyroxinaemia and a delay in nerve conduction velocity were preterm infants who required ventilation, most of the infants with prolonged hypothyroxinaemia and a normal nerve conduction velocity were healthy. Thus it is possible that slow nerve conduction velocity may be caused by a third unmeasured factor associated with illness. An effect of nutrition on growth and myelination cannot be excluded, but the similar weight gain at 40 weeks' postmenstrual age of the infants with and without delayed nerve conduction velocity makes this unlikely.

There is an established association with hypothyroidism and delayed maturation in congenital hypothyroidism and in hypothyroidism in adults.[9 14] Two explanations have been given in these studies for the delayed nerve conduction velocity—delay in myelination and disturbance in the neurotransmitter mechanism.[15]

Previously, there has been no biological evidence that transient hypothyroxinaemia associated with prematurity is harmful, but the question whether treatment is indicated is often raised.[16] These results suggest that transient hypothyroxinaemia may interfere with neurological maturation, as shown by delay in maturation of nerve conduction velocity, and raise the question whether treatment of hypothyroxinaemia may influence the maturation of nerve conduction velocity. Two studies have been reported where treatment for hypothyroxinaemia was given. In one prophylactic treatment with triiodothyronine or thyroxine was used in all preterm infants less than 37 weeks' gestation or below 2200 g, or both, with a fourfold reduction in the mortality in the treated group.[17] In the other study thyroxine was selectively administered for treatment of preterm infants between 25 and 28 weeks' gestation with two or more thyroxine concentrations below 60 nmol/l.[7] The outcome between the treated and non-treated group was not different, but only eight of the 23 infants were seen at follow up. Although the increase in thyroxine concentrations was not different between the two groups, no triiodothyronine concentrations were reported and an increased conversion of thyroxine into triiodothyronine cannot therefore be excluded.

Our aim in the present study was to establish a method that would enable us to measure on a short term basis the biological effect of thyroid function. We were able to show an association between disturbed thyroid function and delay in nerve conduction velocity. Whether this delay is mainly influenced by thyroxine concentrations can best be evaluated by the effect of treatment of hypothyroxinaemia on nerve conduction velocities, and such a prospective study is currently in progress in our unit.

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Carbohydrate derived energy and gross energy absorption in preterm infants fed human milk or formula

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SUMMARY Significant production of breath hydrogen has been shown in premature infants, suggesting limited intestinal capacity for digestion of carbohydrate. To evaluate net absorption of carbohydrate 24 three day balance studies were carried out in seven preterm infants fed pasteurised banked human milk and in 17 preterm infants fed a formula containing 75% lactose and 25% glucose polymers. Because carbohydrate reaching the colon may be converted to organic acids by bacterial flora, carbohydrate net absorption was determined by quantitating the faecal excretion of energy derived from carbohydrate. The carbohydrate derived energy content of milk and stools was calculated as the difference between the measured gross energy and the sum of energy related to nitrogen and fat. Faecal loss of carbohydrate derived energy was lower in the group fed formula (1·9 (SD 1·2) kcal/kg/day) than in the group fed human milk (4·0 (SD 1·8) kcal/kg/day). Net absorption of carbohydrate derived energy was 97·0 (SD 1·9)% as opposed to 92·6 (SD 3·9)%, respectively. Within each group there was no significant relation between carbohydrate energy absorption and fat, nitrogen, or gross energy absorption. Thus, although less complete with human milk than with formula, apparent absorption of energy derived from carbohydrate seemed quite satisfactory in these preterm infants.

Development of intestinal lactase activity occurs late in gestation.[1] According to some studies, virtually all premature infants would be expected to have lactose malabsorption.[2 3]

Carbohydrate absorption in neonates has been estimated by various methods, but these methods often have limitations. Oral tolerance tests[4] require a lot of blood samples and are often unreliable. Measurement of breath hydrogen[2 3] is a sensitive but non-quantitative method of evaluating carbohydrate malabsorption. Determination of lactose assimilation by using stable, isotopically labelled molecules[5] requires sophisticated and expensive equipment. Balance studies with measurements of faecal excretion of carbohydrate[6–8] do not necessarily provide accurate information of intestinal digestibility as carbohydrate reaching the colon may be converted by bacterial enzymatic actions to lactic acid and short chain fatty acids.

In 1982 Kien *et al* developed a method for assessing carbohydrate absorption by measuring gross energy, nitrogen, and fat content of intake and stools.[9] Using this method, we evaluated gross energy and carbohydrate derived energy absorption in preterm infants fed human milk or a preterm formula.

Patients and methods

Twenty four three day balance studies were carried out in 24 preterm boys (Table 1). All infants were

Table 1 *Infant data according to feeding group. Values are mean (SD)*

	Feeding group	
	Human milk	*Preterm formula*
No of infants	7	17
At birth:		
Gestational age (wks)	31 (1)	30 (2)
Weight (g)	1451 (115)	1326 (240)
At balance study:		
Postnatal age (days)	25 (9)	36 (15)
Weight (g)	1787 (246)	1948 (358)

appropriate for gestational age. All were fed orally. At the time of the balance studies, all infants were passing normal stools and were growing at a steady rate. Informed parental consent was obtained.

The balance studies were carried out in seven infants fed pasteurised banked human milk and in 17 infants fed a preterm formula (Pregallia, Gallia, France) containing per dl: protein 1·9 g (whey: casein 60:40), fat 3·36 g (40% medium chain triglycerides), and carbohydrate 9·6 g (75% lactose and 25% maltodextrin). Separate collections of stools and urine were performed with a metabolic bed as previously described.[10] Whenever defecation occurred the stool was immediately frozen. Total nitrogen was determined in both milk and faeces by the micro-kjeldahl technique and fat by a gravimetric method that gives complete recovery of long chain and medium chain triglycerides.[11] Gross energy was determined on lyophilised aliquots of milk and stools using a ballistic bomb calorimeter (Gallenkamp, London, England) as reported elsewhere.[12] The heat of combustion of various nutrients determined in our laboratory was protein 6·15 kcal/g, long chain triglycerides 9·61 kcal/g, and medium chain triglycerides 8·51 kcal/g.[12] The carbohydrate derived energy content of milk and stools was calculated as the difference between the measured gross energy and the sum of calculated gross energy related to nitrogen and fat content. The coefficients of net absorption of nitrogen, fat, carbohydrate derived energy, and gross energy were calcuated as:

(intake—fecal excretion)/intake.

The significance of the difference between two arithmetic means was evaluated by Student's *t* test.

Table 2 *Intake data according to feeding group. Values are mean (SD)*

	Feeding group	
	Human milk	*Preterm formula*
Milk volume (ml/kg/d)	174 (14)	166 (12)
Gross energy (kcal/kg/d)	119·6 (10·2)	136·9 (7·4)*
Total nitrogen:		
(mg/kg/d)	403 (33)	510 (27)*
(kcal/kg/d)	15·5 (1·3)	19·6 (1·0)*
Fat:		
(g/kg/d)	5·17 (0·70)	5·58 (0·31)
(kcal/kg/d)	49·7 (6·7)	53·6 (3·0)
Carbohydrate derived energy		
(kcal/kg/d)	54·4 (6·0)	63·7 (4·5)*

*p<0·05 compared with the group fed human milk.

Table 3 *Faecal excretion data according to feeding group. Values are mean (SD)*

	Feeding group	
	Human milk	*Preterm formula*
Gross energy:		
(kcal/kg/d)	17·3 (5·6)	10·1 (3·3)*
(% of absorption)	85·5 (4·9)	92·6 (2·4)*
Nitrogen:		
(mg/kg/d)	64 (20)	50 (16)
(kcal/kg/d)	2·5 (1·0)	1·9 (1·0)
(% of absorption)	84·1 (4·5)	90·2 (2·9)*
Fat:		
(g/kg/d)	1·12 (0·50)	0·65 (0·27)*
(kcal/kg/d)	10·8 (4·8)	6·2 (2·6)*
(% of absorption)	78·3 (10·0)	88·4 (4·9)*
Carbohydrate derived energy:		
(kcal/kg/d)	4·0 (1·8)	1·9 (1·2)*
(% of absorption)	92·6 (3·9)	97·0 (1·9)*

*p<0·05 compared with the group fed human milk.

Results

Milk volume and fat intake were similar in both groups, but gross energy and nitrogen intakes were significantly higher in the preterm infants fed formula (Table 2). Carbohydrate derived energy intake averaged 54·4 kcal/kg/day in the group fed human milk and 63·7 kcal/kg/day in the group fed formula. In both groups this represented 46% of gross energy intake. The faecal excretions and coefficients of net absorption of gross energy, nitrogen, fat, and carbohydrate derived energy are shown in Table 3. Faecal excretions of gross energy, fat, and carbohydrate derived energy were roughly twice as high in the preterm infants fed pasteurised banked human milk as in those fed formula.

Gross energy absorption averaged 92·6% in the group fed formula as opposed to 85·5% in the group fed human milk. Net absorption of nitrogen, fat, and carbohydrate derived energy was also significantly higher in the group fed formula than in the group fed human milk, these being 90·2, 88·4, and 97·0% as opposed to 84·1, 78·3, and 92·6%, respectively. Within each group, there was no significant relation between carbohydrate derived energy absorption and nitrogen absorption, fat absorption, gestational age, or postnatal age.

Discussion

The aim of this study was to quantitate net absorption of gross energy and carbohydrate derived energy in preterm infants fed human milk or a preterm formula.

In the group fed banked human milk the mean (SD) coefficient of gross energy absorption (86 (5)%) was similar to that reported (87 (5)%) by Whyte *et al* in very low birthweight infants fed their own mother's milk[13] but higher than that found (76 (16)%) by Brooke *et al* in preterm infants fed pasteurised human milk.[14] In the latter study, however, faecal excretion of fat was almost twice as high as in our study or in Whyte's study. In the group fed the preterm formula gross energy absorption (93 (SD 2)%) was slightly higher than that reported (90 (SD 3)%) by Whyte *et al*[13] or by Valman *et al*[15] (87 (SD 5)%) in preterm infants fed formula. Fat absorption was also slightly higher in our infants (88 (SD 5)%), however, than in Whyte's (85 (SD 5)%) or Valman's study (83 (SD 5)%). As in the study of Brooke and Wood,[16] we found a highly significant positive relation between faecal loss of gross energy and faecal excretion of fat (Fig. 1). The good fat absorption in our infants fed formula is probably due to the use of medium chain triglycerides as part of fat, whereas the poor fat absorption observed in some preterm infants fed banked human milk can be explained by the inactivation of lipase (stimulated by bile salt) by pasteurisation.[17] We found that protein net absorption was significantly lower in the group fed human milk than in the group fed formula. This might be due to the presence of poorly degraded immunoglobulins in human milk.[18]

We calculated that net absorption of carbohydrate derived energy averaged 92·6% with human milk and 97% with formula (Fig. 2). There are few published data concerning carbohydrate absorption in neonates. In term infants aged 2 weeks Southgate and Barrett found a net absorption of carbohydrate that averaged 96·9% with breast milk and 99·9% with cow's milk preparation.[6] In very low birthweight infants fed human milk or formula Atkinson *et al* found coefficients of lactose absorption of about 99% during the first weeks of life.[8] Carbohydrate balance studies are, however, notoriously difficult to interpret. In both studies carbohydrate in stools was measured by determination of lactose and reducing substances only. This method does not permit total quantitation of faecal loss of energy derived from carbohydrate because carbohydrate malabsorbed in the small intestine can be converted by colonic flora into short chain organic acids, which are not completely absorbed.[19] In our study the intake and faecal excretion of carbohydrate was calculated from the total energy content less the sum of energy related to measured nitrogen and fat contents. This technique of assessing net absorption of carbohydrate derived energy has the theoretical advantage of taking into account faecal excretion of carbohydrate as well as by products resulting from

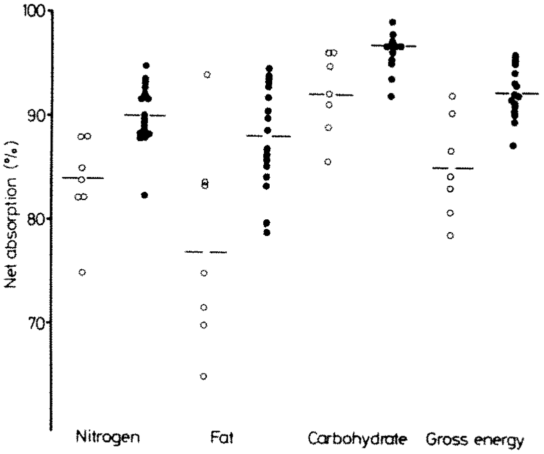

Fig. 2 *Coefficients of net absorption of nitrogen, fat, carbohydrate derived energy, and gross energy in preterm infants fed banked human milk (○) or a preterm formula (●).*

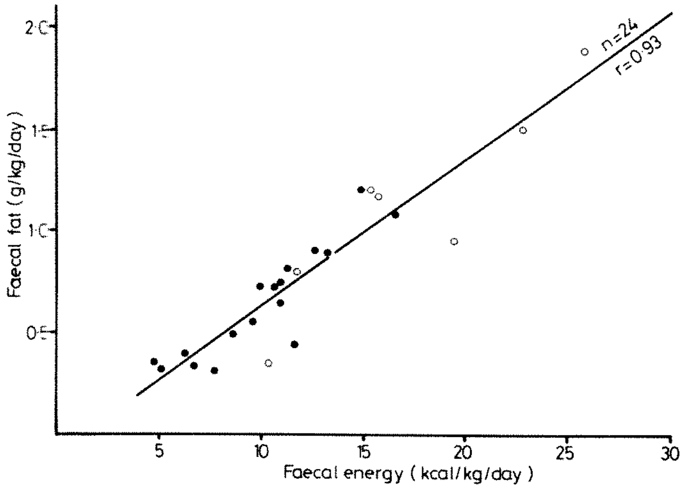

Fig. 1 *Relation between faecal fat and faecal energy in three day stool collections from 24 preterm infants fed banked human milk (○) or a preterm formula (●).*

bacterial degradation of malabsorbed carbohydrate. There are, however, some reservations about this method. Despite the use of freezing, short chain organic acids, which are volatile at acid pH, may have been lost in the process of collection or processing. The assumption that stool fat was present only as long chain triglycerides seems acceptable according to the pattern of newborn faecal lipids.[20] But the assumption that stool nitrogen was present as protein or amino acids only may result in slightly underestimating carbohydrate derived energy as some of the stool nitrogen was presumably also present as urea and ammonia.[9] The calculation of apparent carbohydrate absorption may also be influenced by the faecal excretion of mucus, which is a potentially non-dietary source of stool carbohydrate. Net absorption of carbohydrate derived energy was lower in the group fed human milk than in the group fed formula. This might result from quantitative and qualitative differences in colonic bacteria. Another explanation might be the presence of numerous poorly absorbed oligosaccharides in human milk—2·4 g/dl in colostrum and 1·2 g/dl in mature milk.[21] The mean coefficient of carbohydrate derived energy absorption in the group fed formula containing 75% lactose and 25% glucose polymer was similar to that observed by Kien *et al* in four premature infants fed a formula containing 50% lactose and 50% glucose polymer.[9]

In summary, this study shows that there are differences between net absorption of macronutrients in premature infants fed human milk and preterm formula, resulting in a significantly higher faecal loss of energy with pasteurised human milk. The analysis of production of breath hydrogen by premature infants up to at least 50 days of age has suggested that greater than 66% of dietary lactose may reach the colon.[2] Formulas have been developed, therefore, that contain decreased lactose concentration with carbohydrate energy supplemented with glucose polymer. Our study indicates that overall, in terms of energy, net absorption of carbohydrate is quite satisfactory from either source. Our data, however, give an estimation of 'apparent' as opposed to 'true' absorption of carbohydrate. In the absence of data on serum glucose concentrations, breath hydrogen, or excretion of labelled carbon dioxide it is impossible to determine whether absorption occurred in the small bowel through membranous digestion or in the colon by resorption of short chain organic acids produced by the microflora. This salvage pathway may be important in view of raised excretion of breath hydrogen by infants fed lactose or glucose polymer.[22]

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Osteopenia of prematurity

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SUMMARY Bone mineral content of the forearm was measured by photon absorptiometry in 17 preterm infants at a postconceptional age of 40 weeks. Radiographs of the forearm were assessed by Koo's method and plasma alkaline phosphatase activity was also measured at this time. Bone mineral content was significantly but weakly correlated with Koo score and was not significantly correlated with alkaline phosphatase activity. Neither of these two commonly used investigations accurately predicts the presence of underlying bone disease.

Compared with 15 full term infants the preterm infants had significantly lower values of bone mineral content, palpated ulnar length, and crown-heel length. After adjusting for weight and ulnar length the preterm group still had a significantly lower mean value of bone mineral content than the full term group. Accurate diagnosis of osteopenia of prematurity requires photon absorptiometry, with bone mineral content assessed relative to body weight or ulnar length.

Bone disease (rickets of prematurity or osteopenia) is now being increasingly recognised in surviving preterm infants.[1] Diagnosis is usually based on either radiological abnormalities[2] or rises in plasma alkaline phosphatase activity.[3] Radiological diagnosis is likely to be imprecise because the assessment is subjective and a major loss of bone mineral might have to occur before characteristic changes are apparent.[4] Although raised plasma alkaline phosphatase activity is observed in association with frank radiological rickets,[3] activities change with postnatal age, and it is difficult to decide what activity represents underlying bone disease.[5 6]

Bone mineral content can be measured directly with photon absorptiometry, and we have previously shown that an absorptiometer specifically developed and calibrated for small infants is very precise and accurate.[7] We have compared radiographic and biochemical evidence for bone disease with measurements of bone mineral content in a group of preterm infants on reaching the postconceptional age of 40 weeks, with the aim of assessing the diagnostic accuracy of these two commonly used investigations. We have also compared bone mineral content and other measurements related to body size of preterm infants at 40 weeks with similar measurements of full term infants near the time of birth to assess whether osteopenia of prematurity contains a component that is independent of reduced growth.

Patients and methods

Fourteen boys and three girls born at or before 32 weeks and eight boys and seven girls born at term were investigated after informed parental consent had been obtained. The excess of boys in the preterm group was not the result of selection but reflected the population in the neonatal unit when the study was undertaken. Sex, gestational age, and weight at birth are given in Tables 1 (preterm infants) and 2 (full term infants). Gestational age was assessed according to the mother's last menstrual period and clinical criteria at birth. Investigations were performed within five days of the postconceptional age of 40 weeks in the preterm infants and less than three days after birth in the full term infants. The investigations, which were carried out with the approval of the hospital ethics committee, comprised for the preterm group photon absorptiometry (involving measurement of ulnar length) and radiography of the forearm and measurement of crown-heel length and plasma alkaline phosphatase activity and for the full term group photon absorptiometry and measurement of crown-heel length; radiographs were not taken in the full term group for ethical reasons. All infants received supplemental vitamin D (400 IU daily) with oral feeds using a proprietary milk formula (Osterfeed).

The bone mineral content of the right forearm

Table 1 *Observations on the preterm infants at birth and at the postconceptional age of 40 weeks*

Case No	*Sex*	*At birth*		*At 40 weeks*					
		Gestational age (weeks)	*Weight (g)*	*Weight (g)*	*Bone mineral content (mg/cm)*	*Koo score*	*Alkaline phosphatase (KA units)*	*Ulnar length (mm)*	*Crown-heel length (cm)*
1	M	28	1250	1520	72·5	1	54·4	62·0	40·0
2	M	32	1400	2600	101·0	0	42·5	70·0	45·5
3	M	32	2000	3250	114·7	0	31·6	77·0	49·0
4	M	31	1800	3900	140·9	0	29·1	77·0	50·7
5	M	29	1300	2500	99·8	1	23·9	69·0	45·0
6	M	30	1300	1830	79·3	1	63·3	67·0	42·3
7	M	28	1450	4005	218·8	0	36·9	85·0	52·7
8	M	32	1850	3650	173·6	0	42·9	79·0	52·5
9	M	32	1550	3375	154·2	1	34·1	77·0	48·5
10	M	29	1550	1875	125·7	1	52·7	65·5	41·6
11	M	29	725	1600	61·8	3	120·0	63·0	39·2
12	F	29	1050	1785	75·9	2	87·0	69·0	42·4
13	M	26	1000	4350	117·7	0	108·0	80·0	54·2
14	F	29	1200	1650	89·3	1	46·2	63·0	42·1
15	F	29	1400	2180	86·0	1	49·5	69·0	44·6
16	M	32	1990	1820	112·0	1	37·7	71·0	42·3
17	M	25	650	3430	103·7	2	88·8	76·0	50·6

Table 2 *Observations on the full term infants at birth*

Case No	*Sex*	*Gestational age (weeks)*	*Weight (g)*	*Bone mineral content (mg/cm)*	*Ulnar length (mm)*	*Crown-heel length (cm)*
1	M	39	3710	194·0	85·0	53·0
2	F	40	3200	172·2	80·0	52·5
3	F	40	4440	205·4	86·0	60·0
4	M	40	3430	201·1	85·0	53·5
5	M	38	2980	188·4	77·0	51·0
6	F	40	3390	192·9	81·5	53·0
7	M	40	4200	196·5	83·5	58·0
8	M	41	3700	202·3	80·0	51·0
9	F	40	4600	222·4	90·0	60·0
10	M	40	3030	214·0	78·0	49·0
11	F	40	2730	182·2	76·0	56·0
12	F	40	3000	176·2	78·0	51·0
13	M	40	3550	182·6	81·0	53·0
14	M	40	3680	202·0	84·0	51·0
15	F	40	3450	177·8	81·0	55·0

bones (expressed as mass of mineral per unit length) was measured by photon absorptiometry at the midpoint of the radius, identified by palpation of the distal ulnar styloid process and the proximal tip of the olecranon. Ulnar length was defined as the distance between these sites, measured with dividers before the scan. A regression equation was used to estimate from the ulnar length the position of the midshaft of the radius relative to the distal ulnar styloid process.[7] Technical details of the absorptiometer and its calibration using postmortem specimens have previously been described.[7] The measured bone mineral content of the radius and ulna together is accurate to ±6 mg (95% confidence limits). Precision, calculated from the duplicate values of bone mineral content obtained during every investigation, was 5% in the two groups combined.

At the same time as the bone mineral content was measured an anteroposterior radiograph of the right forearm was taken in the preterm infants under standardised radiographic conditions. The radiographs were assessed, with infant identification obscured, by a radiologist (RA) using the scoring method of Koo *et al.*[2] Grade 0 was allocated to infants with normal bones, 1 to those with mineral rarefaction only, 2 to those with fraying and cupping of the metaphyses—that is, abnormalities observed in rickets, and 3 to those who also had fractures.

A blood sample was obtained from each preterm infant on the same day and assayed for plasma alkaline phosphatase activity[8] using a Technicon analyser (type RA 1000).

Crown-heel length was measured with a standard infantometer.

Statistical analysis of the data included Student's *t* test, Pearson's correlation coefficient, and analysis of variance and covariance. Two tailed probabilities are given throughout.

Results

Table 1 contains the observations on the preterm infants at a postconceptional age of 40 weeks. Table 2 contains the reduced set of observations on the full term infants shortly after birth.

Table 3 *Correlation matrix of observations on the preterm group*

	Gestational age at birth	*Weight at birth*	*Weight at 40 weeks*	*Bone mineral content*	*Koo score*	*Alkaline phosphatase*	*Ulnar length*
Weight at birth	0·79‡						
Weight at 40 weeks	NS	NS					
Bone mineral content	NS	NS	0·73‡				
Koo score	NS	−0·66†	−0·60*	−0·61†			
Alkaline phosphatase	−0·61†	−0·79‡	NS	NS	0·61†		
Ulnar length	NS	NS	0·94‡	0·82‡	−0·58*	NS	
Crown-heel length	NS	NS	0·98‡	0·73‡	−0·62†	NS	0·94‡

*p<0·05. †p<0·01. ‡p<0·001.
NS=Not significant.

Internal relations between observations in preterm infants. Table 3 is a correlation matrix of the measurements on the preterm infants. Bone mineral content was not significantly correlated with weight at birth but was highly significantly correlated with weight at 40 weeks, ulnar length, and crown-heel length (p<0·001). Bone mineral content was significantly correlated with Koo score (p<0·01) but not with plasma alkaline phosphatase activity. In contrast, Koo score was significantly correlated with weight at birth (p<0·01), weight at 40 weeks (p<0·05), and plasma alkaline phosphatase activity (p<0·01). Plasma alkaline phosphatase activity was significantly inversely correlated with gestational age (p<0·01) and weight at birth (p<0·001).

Comparison of preterm and full term groups. Table 4 contains the mean values, standard deviations, and standard errors of the measurements for the preterm and full term groups, with the results of *t* tests. At 40 weeks preterm infants tend to be shorter, weigh less, and have a lower bone mineral content than full term infants.

Table 5 contains the results of analysis of variance and covariance of ulnar length. Both maturity and weight at 40 weeks are significant sources of variation in ulnar length (p<0·001). When measurements of ulnar length are adjusted for weight at 40 weeks a significant difference remains between the groups (p<0·001). For a given weight, preterm infants tend to have shorter forearms and lower values for crown-heel length (p<0·001) than full term infants.

Given that preterm infants are generally shorter and lighter than full term infants at 40 weeks (Table 4), the same approach was used to establish whether, when both weight at 40 weeks and ulnar length are taken into account, a difference in bone mineral content still exists between the groups. These results are also given in Table 5. The difference between the adjusted mean values remains highly significant (p<0·005), indicating that

Table 4 *Comparison of the mean values of the observations on preterm and full term infants*

Variable	*Preterm group (n=17)*			*Full term group (n=15)*			*t Value*	*p Value*
	Mean	*SD*	*SE*	*Mean*	*SD*	*SE*		
Gestational age at birth (weeks)	29·53	2·12	0·52	39·83	0·75	0·19	−18·7*	<0·001
Weight at birth (g)	1380	395	96	3539	543	140	−13·0	<0·001
Weight at 40 weeks (g)	2666	972	236	(3539)	(543)	(140)	−3·1	<0·01
Bone mineral content (mg/cm)	113·3	40·3	9·8	194·0	14·3	3·7	−7·7*	<0·001
Koo score	0·88	—	—	—	—	—	—	—
Alkaline phosphatase (KA units)	55·8	28·4	6·9	—	—	—	—	—
Ulnar length (mm)	71·74	6·77	1·64	81·73	3·84	0·99	−5·0	<0·001
Crown-heel length (cm)	46·07	4·83	1·17	53·80	3·37	0·87	−5·2	<0·001

**t* Test with unequal variances.

Table 5 *Results of analysis of variance and covariance of ulnar length and bone mineral content*

(a) Sources of variability in all 32 infants, including maturity.

Variable	*Source of variation*	*Mean square*	*F*	*p Value*
Ulnar length	Weight at 40 weeks (g)	1487·3	321·2	<0·001
	Maturity	114·4	24·7	<0·001
	Residual	4·6	—	—
Bone mineral content	Weight at 40 weeks (g)	1934	4·7	<0·05
	Ulnar length (mm)	18428	44·9	<0·001
	Maturity	4233	10·3	<0·005
	Residual	410	—	—

(b) Group mean values unadjusted and adjusted for weight at 40 weeks.

Variable		*Preterm group*	*Full term group*	*p Value*
Ulnar length	Unadjusted	71·74	81·73	<0·001
	Adjusted	74·38	78·73	<0·001
Bone mineral content	Unadjusted	113·3	194·0	<0·001
	Adjusted	134·3	170·3	<0·005

the bones of preterm infants are disproportionately undermineralised even when allowance is made for body size.

Discussion

The terminology used in neonatal bone disease is confusing. Rickets of prematurity implies the presence of radiologically detectable abnormalities at the ends of the long bones and is historically related to vitamin D deficiency.[9] These abnormalities, however, can occur in neonates, despite normal plasma vitamin D concentrations.[1] Osteopenia of prematurity, while a better term than rickets, implies a deficit in bone mineral that is difficult to quantify radiologically.

In preterm infants we found a significant but weak relation between radiological appearance and bone mineral content at a postconceptional age of 40 weeks. Four of the six infants with a normal Koo score had bone mineral content values between 3·7 and 6·5 standard deviations below the mean for infants born at term. Previous work on adult bones has shown that substantial demineralisation has to occur before radiological changes become apparent,[4] and our results further emphasise the limitations of radiological assessment even if a standardised scoring system is used. To depend on radiology for the diagnosis of osteopenia will result in serious underestimation of the extent of this condition. Furthermore, therapeutic studies aimed at correction either by using vitamin D supplements or by enhancing substrate intake may give misleading results if undue reliance is given to apparent radiological improvement. Although calcium supplementation has been shown to result in radiological improvement,[10] the lack of precision of radiological assessment is such that small changes in bone mineral content are unlikely to be detected.

At a postconceptional age of 40 weeks the preterm infants in this study were lighter and shorter than infants born at 40 weeks. Although the mean bone mineral content for the preterm group was reduced relative to the full term group, this could have been the result of preterm infants having smaller bones, because bone mineral content is dependent on size.[11] When analysis of variance was used to correct for both weight and ulnar length, however, the mean bone mineral content was still significantly reduced in the preterm group. The observed reduction in bone mineral content cannot be explained solely on the basis of body size and must therefore contain a component due to underlying metabolic bone disease.

Plasma alkaline phosphatase activity increases with postnatal age, and peak values are found at a time near to what should have been term.[3] Many variables affect its assay,[5] and the range of values in infants with radiological bone disease overlaps the range in those with normal bones to such an extent that absolute values are of limited use.[6] Although we found alkaline phosphatase activity to be related to Koo score, it was not significantly correlated with bone mineral content. It has been suggested that activities up to five times the upper limit of the adult range should be regarded as normal in growing preterm infants, while activities exceeding six times the upper limit (which for our laboratory is 13 KA units) are suggestive of underlying radiological bone disease.[5] In our study three of the four infants whose plasma alkaline phosphatase activity exceeded 78 KA units had abnormal Koo scores, and two had particularly low values of bone mineral content. While very high plasma alkaline phosphatase activities may occur in association with frank radiological bone disease, however, normal activities are also found in those with osteopenia. Thus neither radiological assessment nor plasma alkaline phosphatase activity can reliably detect undermineralisation in the bones of growing preterm infants. At present photon absorptiometry, although primarily a research tool, seems to be the only viable technique for diagnosing osteopenia of prematurity.

Although the mean gestational age of the preterm infants was just under 30 weeks, many considerably less mature infants now survive. Only two of the 17 infants in our preterm group had bone mineral content values within the norml range for infants born at term. It is more than likely therefore that any infant born before 28 weeks will develop osteopenia even in the absence of obvious radiological or biochemical abnormalities. Sequential measurements of bone mineral content in premature infants have shown that the postnatal increase in bone mineral content is significantly less than that expected in utero,[12 13] and while the long term consequences are unknown this problem and its treatment merit further investigation.

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Small for dates babies: are they really a problem?

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SUMMARY One hundred and sixty four infants <5th centile for gestation specific birth weight were born at gestations ≥37 weeks in the Cambridge Maternity Hospital in 1982. Of these, 60 were <2·3rd centile—that is, >2 standard deviations below mean birth weight. Serious disease was rare: only six (4%) had recognisable malformations. There was only one neonatal death, a baby <2·3rd centile with the Neu-Laxova syndrome. Nine (5%) became hypoglycaemic but with no serious symptoms: one of these was already on the neonatal unit with respiratory distress syndrome and was given intravenous dextrose, and the remaining eight all responded to milk feeds. Only 13 out of the 164 patients (8%) were admitted to the neonatal unit, eight of the 12 survivors for 48 hours or less.

Small for dates babies of 37 weeks' gestation or more pose few neonatal problems and can be safely cared for on a postnatal ward.

In the past small for dates babies have caused appreciable concern to their medical attendants. According to the 1958 perinatal mortality survey infants with birth weight ≤2500 g born after full duration or prolonged pregnancies had a mortality eight times higher than those weighing >2500 g.[1] The danger of symptomatic hypoglycaemia was first recognised in 1959.[2] Many other neonatal complications, such as birth asphyxia, hypothermia, sepsis, polycythaemia, pulmonary haemorrhage, and an increased risk of congenital abnormality, have been reported in small for dates infants.[3] Ounsted *et al* found that only 35% of a cohort of infants more than 2 standard deviations below the mean birth weight for gestation had an uncomplicated neonatal course, and their neonatal mortality was 63 per 1000 live births.[4] In recent years, however, our impression has been that with improved standards of obstetrics and routine neonatal care, small for dates infants other than those with complications attributable to short gestation have caused few problems.

Patients and methods

It is our policy to admit to the neonatal unit only babies who have symptoms or who weigh <1800 g; asymptomatic babies above this weight go to the postnatal wards irrespective of gestation or whether they are small for dates or not.

Since 1975 the routine on the postnatal wards in the Cambridge Maternity Hospital has been to record Dextrostix (Ames, United Kingdom) routinely at 2, 6, 12, 24, 36, and 48 hours of age in all babies below the 2·3rd centile. Dextrostix are performed in bigger infants at the discretion of the nursing or medical staff. As well as having these Dextrostix measurements the babies receive 60 ml/kg of formula on day 1 and 90 ml/kg on day 2, plus whatever they receive from the breast.[5] In this study we have reviewed all 164 infants born in 1982 at Cambridge Maternity Hospital at gestations of 37 or more weeks (259 days or more) whose birth weights were below the fifth centile of Tanner and Thomson.[6] These infants were termed 'small for dates. The mothers' and infants' notes were scrutinised for the presence of an antenatal diagnosis of poor growth, intrapartum asphyxia, intubation at birth, hypothermia (<36°C), hypoglycaemia (glucose concentration <1·4 mmol/l (25 mg/100 ml on Dextrostix)), need for admission to the neonatal unit, and any neonatal illness.

For analysis, infants were divided into those above or below the 2·3rd centile of Milner and Richards[7] (equivalent to 2 SD below the mean birth weight for gestation). The χ^2 test was used for comparing frequency distributions using Yates's correction for small numbers.

To extend our assessment of the safety of our practice we reviewed our records to find all those infants admitted to our neonatal unit with symptomatic hypoglycaemia during the six year period 1977–82, during which our postnatal ward routine was that described above.

Results

1982 data. Intrauterine growth retardation was predicted in only 30% of singleton infants <5th centile, rising to 44% of those <2·3rd centile. No baby, however, was born severely asphyxiated, and of the 15 who needed intermittent positive pressure ventilation in the labour ward all were in good condition and breathing spontaneously by 10 minutes of age. One of these 15 infants, weighing 1910 g and born at 37 weeks' gestation, was observed on the neonatal unit for 24 hours. Of eight stillbirths in 1982 more than 37 weeks' gestation, there were two with malformations (Potter's syndrome and isolated hydrocephalus), both of whom were of normal birth weight. The only small for dates stillbirth had been diagnosed antenatally as growth retarded, and although the mother was given a 'kick' chart and instructions, she failed to contact the hospital when fetal movements fell into the danger zone.

The neonatal problems are summarised in Table 1. Thirteen infants (8%) were admitted to the neonatal unit for the reasons shown in Table 2, and all of them were admitted from the labour ward immediately after delivery. Of the 11 babies who were not malformed who were initially admitted to the unit, eight had been discharged to the postnatal ward by 48 hours. Six infants (4%) had a malformation recognised in the neonatal period (ventricular septal defect, Neu-Laxova syndrome, Werdnig–Hoffman disease, multicystic kidney, imperforate anus, and agenesis of the pinna), but only two of these, the baby with an imperforate anus and the case of Neu-Laxova syndrome, were admitted to the unit.

Table 1 *Mortality and gross morbidity in 164 infants born in 1982 at Cambridge Maternity Hospital at gestations ≥37 weeks with birth weights below the 5th centile. Numbers in brackets are percentages*

	Birthweight centile		*Total*
	2·3rd–5th	*<2·3rd*	
Total live births	104	60	164
Twins	15	6	21
Malformations	4	2	6
Admitted to neonatal unit	6 (6)	7 (12)	13 (8)
Hypothermia <36°C	16 (15)	21 (35)	37 (27)
Hypoglycaemia <1·4 mmol/l	3 (3)	6 (10)	9 (5)
Neonatal deaths	0	1*	1†

*Neu-Laxova syndrome.
†6/1000 live births.

Table 2 *Reasons for admission to neonatal unit and duration of stay in infants ≥37 weeks' gestation (n=164)*

Diagnosis	*No of infants*	*Duration of stay (d=days, h=hours)*
Birth weight <1800 g	2	4h, 2d
Major malformation	2	One died, one sent to another hospital
Respiratory distress syndrome	1	12d
Group B streptococcal sepsis	1	6d
Transient tachypnoea	2	2d, 4d
Meconium aspiration	2	1d, 2d
Hypothermia	2	12h, 24h
Birth asphyxia	1	24h
Total admissions	13	

Hypothermia. As shown in Table 1, 37 of the 164 infants (23%) had recorded temperatures below 36°C. The incidence of this problem rose to 21 of 60 infants (35%) below the 2·3rd centile. This may be an underestimate of the incidence of hypothermia as 42% had no temperature recorded in their notes. Only six (4%), however, had temperatures below 35°C, the lowest being 34°C. The lowest temperatures were virtually always those recorded in the first few hours of life while the infant was on the labour ward or shortly after admission with his mother to a postnatal ward. The temperatures all rose steadily thereafter, and no symptoms attributable to cold were seen. Two infants were admitted to the neonatal unit, however, because of their low temperature (Table 2).

Hypoglycaemia. Measurements were available in only 72% of infants <5th centile but were recorded in 88% of those below the 2·3rd centile. Concentrations of glucose below 1·4 mmol/l (25 mg%) were found in only nine infants, three of the 104 infants (3%) with birth weights between the 2·3rd and 5th centile, and six of the 60 (10%) below the 2·3rd centile. The three infants with birth weights between the 2·3rd and 5th centiles were all on the postnatal ward, and their blood glucose concentration increased and remained normal after an extra milk feed. Of the six infants <2·3rd centile, there were five on the postnatal ward whose blood glucose concentrations rose with an extra feed. The sixth, already on the neonatal unit with transient tachypnoea of the newborn, was started on intravenous dextrose. Of these nine babies, eight were asymptomatic, and one was described as jittery. Thus no infant had serious symptoms from hypoglycaemia, and no infant was admitted to the neonatal unit solely for correction of hypoglycaemia.

1977–82 data. Out of nearly 23 000 infants bor the Cambridge Maternity Hospital at 37 we gestation or greater, there were 10 infants symptomatic hypoglycaemia. Of these, three fits, two had mild respiratory illness and were found coincidentally to have a blood glucose concentration $<1\cdot1$ mmol/l, and the other five were just jittery. Only two, both of whom were jittery, were small for dates, and only one of these required intravenous dextrose to keep his glucose concentration $>1\cdot1$ mmol/l. Both have developed normally. The three infants with fits all weighed more than 3000 g (3100, 3300, and 3400 g), and apart from poor feeding no cause was ever found for their hypoglycaemia.

Discussion

Neonatal mortality in this study of 164 term, small for dates infants was limited to a single grossly malformed infant, and neonatal morbidity from acquired illness was uncommon and transient. If hypothermia is considered as being only below 35°C and birth asphyxia as only intermittent positive pressure ventilation beyond five minutes then the total morbidity was 31 of 164 infants (19%), comprising six malformations, seven cases of birth asphyxia (one also of hypothermia), nine cases of hypoglycaemia (one each also of hypothermia and transient tachypnoea), four cases of isolated hypothermia, and five other admissions to the special care baby unit (three with respiratory symptoms and two solely for low birth weight). This is considerably less than has been reported in other series. This low incidence of complications was not due to growth retarded fetuses dying in utero. Despite the fact that most growth retarded infants were not recognised antenatally, the overall improvements in the general standard of intrapartum care and neonatal resuscitation in the last two decades must have contributed to the low incidence of complications such as hypoxic ischaemic encephalopathy, meconium aspiration, infection, and massive pulmonary haemorrhage, which traditionally are supposed to occur in growth retarded infants.

Small babies with a large surface area to body weight ratio are prone to hypothermia. The body temperature of too many babies in this study fell below 36°C, usually while the infant was still on the labour ward. Improved labour ward procedures as a result of this study and a move to a new, better designed hospital have resulted in this problem virtually disappearing.

There remains a major anxiety in the minds of most paediatricians about hypoglycaemia in small for dates infants. This anxiety was created by the much cited studies of Neligan[8] and Lubchenko and Bard,[9] who reported an incidence of hypoglycaemia (presumed asymptomatic) of over 20% in growth retarded infants, and by studies such as those of Anderson *et al*,[10] Cornblath *et al*,[2] Koivisto *et al*,[11] and Pildes *et al*,[12] reporting a high incidence of severe sequelae and neuropathological changes in infants who, as neonates, had symptoms attributed to hypoglycaemia.

It has to be emphasised, however, that most of these studies were from an era when neither early feeding of small for dates infants was pursued with the enthusiasm that was fostered by the studies of Smallpiece and Davies[13] nor monitoring for asymptomatic hypoglycaemia in small for dates infants by Dextrostix was routine. In 1982 we reported a very low incidence (5/167 (3%)) of asymptomatic hypoglycaemia using the above protocol in infants with a birth weight of 1800–2500 g (about half of whom were small for dates) nursed on a postnatal ward.[14] A similarly low incidence of hypoglycaemia in adequately fed small for dates infants was reported by Walther and Ramaekers.[15]

This present study, provoked, in part, by the persisting controversy over our 1982 data that adequately fed and monitored small for dates babies could be safely cared for on a postnatal ward, confirms that even asymptomatic hypoglycaemia is rare (9/164 (5%)) in small for dates infants. Those who are asymptomatic and with their mothers on a postnatal ward respond promptly to an extra feed. No small for dates infant in this study or that of Whitby *et al*[14] developed symptomatic hypoglycaemia.

As it is uncertain whether jitteryness is a specific feature of neuroglycopenia or whether it is caused by 'smallness-for-dates' itself, we failed to diagnose hypoglycaemia before symptoms (fits) occurred in only three infants in the six year period 1977–82. None of them was below even the 10th birthweight centile for gestation, and none would, therefore, have been included in any currently recommended screening programme for detecting hypoglycaemia in small for dates infants.

Whether we missed any cases of asymptomatic hypoglycaemia in the period 1977–82 remains speculative. As there is no evidence that asymptomatic hypoglycaemia is associated with any long term sequelae[3] we believe that detecting a biochemical abnormality of no clinical importance—that is, transient self correcting asymptomatic hypoglycaemia—serves no purpose. Furthermore, the data show that no small for dates infant with asymptomatic hypoglycaemia can have subsequently developed symptomatic hypoglycaemia (fits) in this six year period.

In the 1977–82 data only one infant was found with a weight between the 2·3rd and 5th centile who became hypoglycaemic and who required any treatment other than an extra feed to maintain a normal blood glucose concentration. As this baby was detected on clinical grounds, and as the blood glucose concentration in all the other infants in this birthweight band who developed asymptomatic hypoglycaemia rose to normal after a feed, we see no point in routinely screening any small for dates infants >2·3rd centile for birth weight for hypoglycaemia. Infants above this centile, however, irrespective of how far they are above this centile, who look wasted and malnourished, feed poorly, or develop appropriate symptoms, such as apnoea, pronounced jitteryness, and fits, should have their blood glucose concentration measured promptly.

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Reduction of skin damage from transcutaneous oxygen electrodes using a spray on dressing

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SUMMARY A spray on, copolymer acrylic dressing (Op-Site) was used to limit the skin damage caused by a transcutaneous oxygen electrode and its adhesive ring. Two identical electrodes were applied to the abdominal skin of 10 preterm infants, one on untreated skin, the other after application of Op-Site. It was found that Op-Site prevented the epidermal damage (as measured by transepidermal water loss) that occurs when the adhesive ring is removed from untreated skin. It did not interfere with transcutaneous oxygen measurements; absolute values and response times were unchanged. Op-Site is therefore useful in preventing the skin trauma that occurs when transcutaneous oxygen monitoring is being performed in preterm infants below 30 weeks' gestation in the first week of life. Care must be taken, however, to prevent a build up of Op-Site—it should be applied as a single layer, allowed to dry, and removed after use.

Skin surface probes are widely used to monitor heart rate, respiratory rate, temperature, and blood gases in sick preterm infants. Such monitoring, though, is not strictly non-invasive. All surface probes need to be secured to the skin with adhesive tape, which strips off the superficial layer of the stratum corneum when it is removed. Although this is of little importance in a term infant, it is of tremendous importance in the very preterm infant below 30 weeks' gestation, whose stratum corneum is thin and poorly developed. Transepidermal water loss increases, absorption of topically applied chemicals occurs more readily, and the stripped area may provide a site for the entry of micro-organisms.[1]

Heated transcutaneous gas electrodes cause the most damage to the preterm infant's skin. The skin in contact with the heated electrode suffers the changes of an early burn, the surrounding skin is damaged by stripping when the adhesive ring is removed, and as the electrode site is usually changed every four hours a large area of skin is subjected to trauma. The neonatal unit at King's College Hospital, London, have used a spray on dressing, Op-Site Spray Dressing (Smith and Nephew, United Kingdom), to limit the skin damage caused by transcutaneous oxygen monitoring. Op-Site is an acrylic copolymer in an ethyl acetate and acetone solvent, which forms a flexible film when sprayed on to the skin. This film is permeable to water vapour and gases.

The aim of this study was to see whether Op-Site protects the preterm infant's skin from damage by the probe and to examine whether or not it interferes with transcutaneous oxygen monitoring.

Subjects

Ten preterm infants were studied. Their gestation ranged from 26 to 31 weeks (mean (SD) 28·4 (1·8)), their birth weight from 950 to 1560 g (mean (SD) 1·2 (0·26)), and their age from 1 to 7 days (mean 3·8). All infants were clinically stable and were studied with their mothers' permission. The study was approved by the hospital's ethical committee.

Methods

Investigation of monitor function. Two identical transcutaneous oxygen electrodes (Radiometer TCM2, Copenhagen, Denmark) were calibrated in air at 43°C. They were placed on undamaged skin on either side of the upper abdomen of preterm infants—one on untreated skin, the other on skin sprayed for one to two seconds with a layer of Op-Site, which was allowed to dry before application of the electrode. Fifteen minutes after application the electrode readings were compared. Readings and response times were then compared when the infant's inspired oxygen concentration was increased by 20% and then reduced to the original concentration. Response times were measured as the time taken for the transcutaneous oxygen reading to restabilise after the inspired oxygen concentration had been changed. The electrodes were left in place for four hours while continuous transcutaneous oxygen recordings were made.

Investigation of skin damage. Transepidermal water loss in g/m^2/h was measured at both skin sites before the electrodes were applied using an Evaporimeter (Ep 1, Servomed, Sweden) as previously described.[2] Transepidermal water loss was then measured from both sites 30 minutes, four hours, and 12–16 hours after removal of the electrodes. Two measurements of transepidermal water loss were made after removal of the electrodes, one from the central area of skin in contact with the heated electrode and one from the surrounding skin in contact with the adhesive ring used to fix the electrode in place.

Analysis. Statistical analysis was by paired Student's *t* test and by Mann-Whitney U test.

Results

Transcutaneous oxygen readings were similar from both electrodes and showed no significant difference, and the response times of the two electrodes were identical (Fig. 1). Two factors, however, did affect the transcutaneous oxygen readings. Transcutaneous oxygen readings were lower from skin that had had several layers of Op-Site applied than from untreated skin. In one of the infants studied the transcutaneous oxygen tension from the treated skin after four Op-Site applications was about 10 mm Hg lower than at the control site and about 20

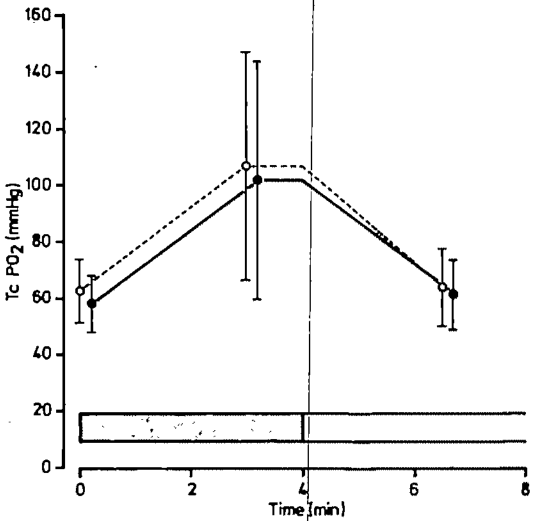

Fig. 1 *Mean (SD) transcutaneous oxygen tensions ($TcPO_2$) (mm Hg) from skin treated with Op-Site (●) and untreated skin (○) when the inspired oxygen concentration was increased (shaded area) and then decreased (blank area).*

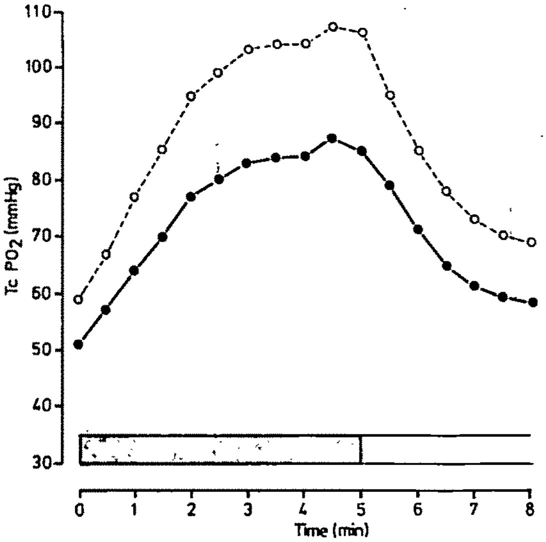

Fig. 2 *Transcutaneous oxygen tensions ($TcPO_2$) (mm Hg) recorded from one infant when the inspired concentration was increased (shaded area) and decreased (blank area). Readings from the skin treated with four layers of Op-Site (●) were lower than from untreated skin (○).*

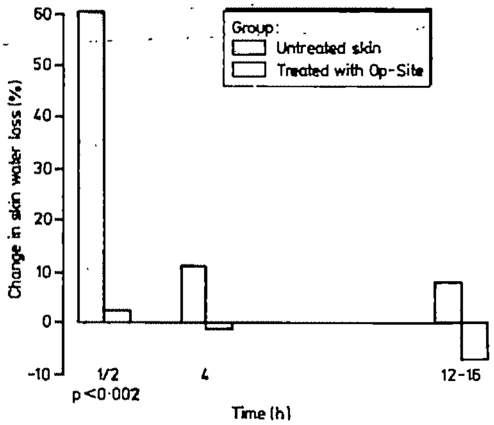

Fig. 3 *Change in water loss (%) from the central area of skin in contact with the heated electrode. The initial high water loss in the untreated group was the result of hydration of the stratum corneum by the contact solution and not the result of epidermal damage.*

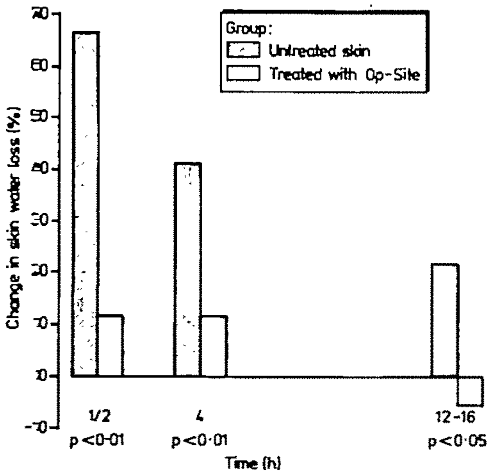

Fig. 4 *Change in water loss (%) from the stripped area of skin in contact with the adhesive ring. The persistently high water loss in the untreated group was the result of damage to the stratum corneum.*

mm Hg lower when the infant's inspired oxygen concentration was increased (Fig. 2). It was also discovered that if the Op-Site was not allowed to dry before the electrode was applied the solvent affected the oxygen permeability of the electrode membrane, giving falsely high transcutaneous oxygen values.

The percentage change in transepidermal water loss after removal of the electrode was calculated by comparison with the transepidermal water loss before the electrode was applied. Transepidermal water loss was high from the central area of skin 30 minutes after removal of the electrode from the untreated site but not from the site treated with Op-Site (Fig. 3), but by four hours the difference was small and not significant. Transepidermal water loss from the skin in contact with the adhesive ring was significantly higher from the untreated skin compared with the skin treated with Op-Site where the rise in transepidermal water loss was small. This difference was still present 12–16 hours later (Fig. 4).

There was no difference in the disappearance of the central erythema caused by the heated electrode at the treated and untreated sites. Only one mild first degree burn was seen, and this was on untreated skin.

Discussion

Op-Site spray dressing, when thinly applied, does not interfere with the normal functioning of a transcutaneous oxygen electrode, suggesting that the film is readily permeable to oxygen. This is consistent with previous unpublished observations where we have shown that the thin copolymer layer is permeable to water vapour, carbon dioxide, and oxygen. In the two studies in which more than one layer of Op-Site was applied, however, transcutaneous oxygen measurements were artificially low (as in Fig. 2).

We were unable to show a protective effect of Op-Site on that part of the skin that was in direct contact with the heated electrode.

The transiently high transepidermal water loss seen in the untreated skin after removal of the electrode is probably due to loss of water from the stratum corneum, which has been hydrated by the contact solution. This rapid rate of fall in transepidermal water loss is seen when other water containing preparations are applied to the skin[3] and when the stratum corneum is drying out in the first few hours after delivery.[4] Erythema of the skin was mild and transient in both groups, with only one minor burn occurring. We noted, though, that Op-Site abolishes the sensation of heat when the heated electrode is applied to adult skin and it might be expected to reduce the incidence of burns that are occasionally seen with use of the electrode in preterm infants.[5 6]

Op-Site has an appreciable protective effect on the skin that is in contact with the adhesive ring used to hold the electrode in place. The persistent increase in transepidermal water loss seen in untreated skin is an indication of damage to the stratum corneum caused by stripping. No such damage occurs with the use of Op-Site. Damage to the stratum corneum from stripping is only important in infants below 30 weeks' gestation in the early neonatal period as this is the time when the epidermal barrier is thin, poorly keratinised,[7] and readily permeable to water vapour and chemicals.[1] It has been estimated that in such infants, who often have several monitoring probes applied to their skin at any given time, 15% of the body's skin can be traumatised by adhesive stripping each day[1] (assuming that transcutaneous gas electrodes are moved every four hours). Besides increasing difficulties in fluid balance and temperature control and the increased risk of poisoning from topically applied agents, secondary skin sepsis may occasionally occur and it is possible that bacteria can enter the body at these sites.

Is it safe to apply Op-Site to the skin of very preterm infants? We observed no local or systemic effects, and it is unlikely that the high molecular weight acrylic copolymer could be absorbed. The solvent quickly evaporates after application of the spray dressing, too quickly for absorption to take place. Our study shows that Op-Site protects the skin from adhesive stripping without interfering with transcutaneous oxygen monitoring and could therefore be used with benefit in the most vulnerable infants (below 30 weeks' gestation and less than 1 week old). The finding that underreading of transcutaneous oxygen values occurs if several layers of Op-Site are interposed between electrode and skin, however, is potentially dangerous. To avoid this, the following procedure may be followed. The can of Op-Site is shaken and then held inverted over the skin at a distance of about 10 cm. A one to two second spray is applied to a circle of skin slightly larger than the adhesive electrode ring, using a cardboard or plastic template with a suitable hole cut in it: this limits the Op-Site to the desired area. It must then be allowed to dry for three or four minutes before the electrode is applied. When the electrode is removed the copolymer dressing under the adhesive ring will be removed with it. Any surplus Op-Site can be removed with an isopropyl swab. If Op-Site is repeatedly applied and not removed several layers of copolymer may be built up, which can cause serious underestimation of transcutaneous oxygen tensions.

We are grateful to Dr D Curnock and Professor A Milner for allowing us to study infants under their care and to V A Howe Ltd (London) for lending us the transcutaneous oxygen monitor. N J Evans was supported by a grant from the Medical Research Council of Great Britain. We are grateful to Dr Harold Gamsu, Consultant Neonatologist at King's College Hospital, London, who suggested that the use of a protective spray on dressing should be examined.

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Abnormal radial artery in Down's syndrome

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SUMMARY Abnormal arterial patterns in the forearm were discovered in 12 of 77 patients (16%) with Down's syndrome. Eight patients had an enlarged anterior interosseous artery, the distal portion of which was palpable over the dorsum of the hand; in seven it was associated with absence of the radial artery and in one it coexisted with the radial and ulnar arteries. Three patients had a hypoplastic radial artery and a relatively dominant ulnar artery. One patient had a vestigial radial artery that ended as muscular branches in the forearm. The developmental aspects of these aberrations are discussed.

The radial artery in its superficial position on the volar aspect of the wrist offers a well known access for clinical evaluation of the circulation. Its palpable pulsation on the radial side of the wrist between the flexor carpi radialis tendon medially and the bony prominence of the lower part of the radius laterally has been remarkably constant, and reports on variations are scanty.[1 2] Reports on congenital heart diseases in Down's syndrome are ample;[3–8] extracardiac vascular abnormalities, however, have been infrequently described, and radial artery aberrations have not been mentioned. Recent detection of two patients, both with Down's syndrome and congenital heart disease, in whom the radial artery pulsation was not palpable in the usual position over the wrist, prompted us to look at the incidence of this phenomenon.

Patients and methods

From January 1983 to December 1985 a total of 1087 Chinese children were studied. Of these, 510 were otherwise normal children with congenital heart disease and 77 were patients with Down's syndrome (40 boys and 37 girls), of whom 50 had congenital heart disease. Five hundred normal children without heart disease were included as controls.

Each patient was examined independently by at least two paediatricians for the presence of abnormal arterial pulsations in the hand. The radial and ulnar arteries were carefully palpated for on the flexor surface of the wrist and distal forearm. Patients with previous cannulation of either artery were excluded. The radial or ulnar artery was considered abnormal if (a) its pulsation was not

Table *Abnormality of the radial artery and associated congenital heart disease in 12 patients with Down's syndrome*

Case	*Sex*	*Age (yrs)*	*Congenital heart defect*	*Artery abnormalities*		*Side*
				Radial	*Dorsal*	
1	F	1	Ventricular septal defect	Absent	Present	Right + Left
2	F	0·5	Ventricular septal defect	Absent	Present	Right + Left
3	F	0·3	Patent ductus arteriosus, atrial septal defect	Absent	Present	Left
4	F	5	Ventricular septal defect, atrial septal defect	Absent	Present	Right
5	F	2	Ventricular septal defect, patent ductus arteriosus	Absent	Present	Right
6	F	10	Normal	Absent	Present	Right + Left
7	F	1	Atrioventricular canal	Absent	Present	Right + Left
8	F	12	Ventricular septal defect, patent ductus arteriosus	Normal	Present	Right + Left
9	F	4	Ventricular septal defect	Hypoplastic	Nil	Left
10	F	13	Normal	Hypoplastic	Nil	Right + Left
11	M	7	Normal	Hypoplastic	Nil	Right + Left
12	M	0·8	Atrioventricular canal, patent ductus arteriosus	Vestigial	Nil	Right + Left

palpable and no arterial flow could be recorded with a Doppler flow detector in its usual position at the wrist, or (b) the radial pulsation was notably weaker than that of the ulnar artery. Presence of an additional arterial pulsation apart from that of the radial or ulnar artery in another position, particularly over the dorsum of the wrist, was carefully looked for. The cardiac anatomy in those with congenital heart disease was defined by cardiac catheterisation or two dimensional echocardiography, or both. In patients with abnormal arterial pulses the arterial pattern of the forearm was visualised by contrast injection into the subclavian or brachial artery. The subclavian artery was entered through antegrade or retrograde catheterisation of the aorta during cardiac catheterisation.

The brachial artery was cannulated by percutaneous puncture in one patient with atrioventricular canal defect and patent ductus arteriosus before cardiac surgery for monitoring of blood pressure. This method was also used in another patient with clinically weak radial artery pulsations and normal heart for whom cardiac catherisation was not performed. Written consent was obtained from the parents after full explanation of the procedure. In both subclavian and brachial approaches meglumine iothalamate (Conray 280) 0·5 ml/kg body weight was injected by hand at 1–2 ml/sec, and the arteriogram was recorded with cinematography. A subclavian arteriogram was performed during cardiac catheterisation in 10 patients with congenital heart disease but no clinical abnormalities of the radial or ulnar artery pulses for comparison.

Results

In none of the normal children with or without congenital heart disease was an abnormal artery detected clinically. On the other hand, 12 patients (16%) with Down's syndrome were found to have abnormal arteries in the wrist. Nine were seen

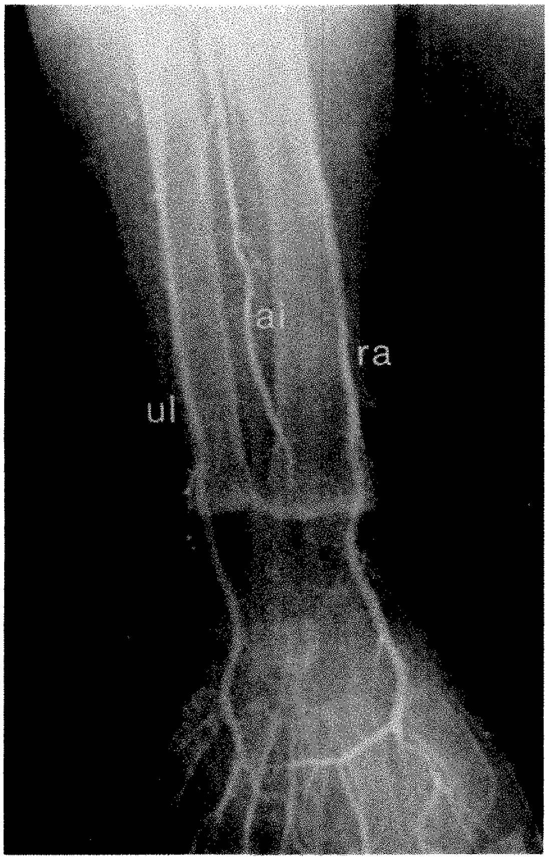

Fig. 1 *Normal arterial pattern of the forearm. ra=Radial artery, ai=anterior interosseous artery, and ul=ulnar artery.*

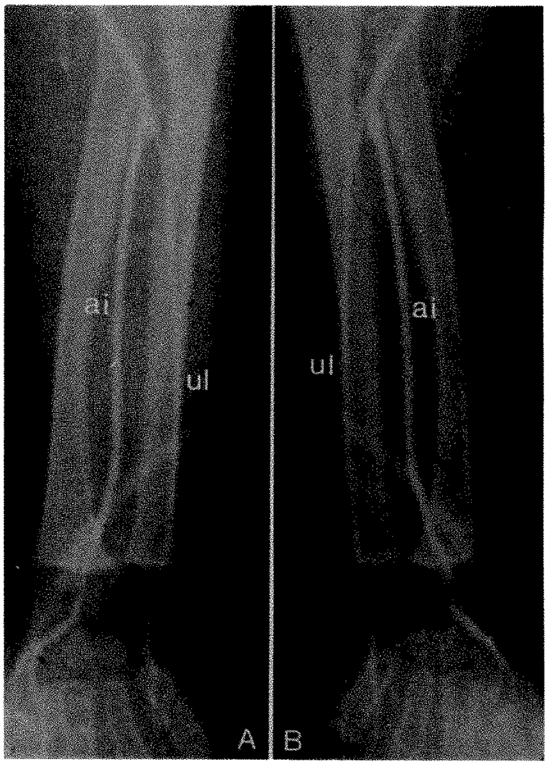

Fig. 2 *Right (A) and left (B) forearm of patient with absent radial artery and enlarged anterior interosseous artery (ai). ul=Ulnar artery.*

among the 50 cases (18%) with congenital heart disease and three among the 27 (11%) with normal hearts; there was no statistical difference between the two groups (χ^2 test). Girls were predominantly affected, comprising 10 of the 12 cases ($0·05 > p > 0·01$). The Table lists the nature of the arterial abnormalities detected and the associated congenital heart diseases.

Figure 1 shows the normal arterial pattern in the forearm in patients with normal radial and ulnar pulsations in the wrist. The radial artery is larger than the ulnar artery and the anterior interosseous artery is a relatively small artery that takes its origin from the ulnar artery and tapers towards the wrist.

Four types of clinical-angiographic abnormalities of the forearm arteries were observed in patients with Down's syndrome. These were as follows.

(1) The most commonly encountered abnormality was an absent radial artery pulsation in the usual position over the wrist but presence of a strong arterial pulsation over the dorsum in the lowermost portion of the forearm, which could be followed caudally over the dorsal aspect of the wrist to enter the first dorsal interosseous muscle. This pattern was seen in seven of the 12 cases. Angiography showed absence of the radial artery and an enlarged anterior interosseous artery in these patients (Fig. 2).

(2) In one patient the dorsal artery was present together with the radial and ulnar arteries (Fig. 3). The radial artery, however, did not course round the wrist to the back of the hand as it usually behaves.

In both the above groups the dorsal artery represents the distal portion of the anterior interos-

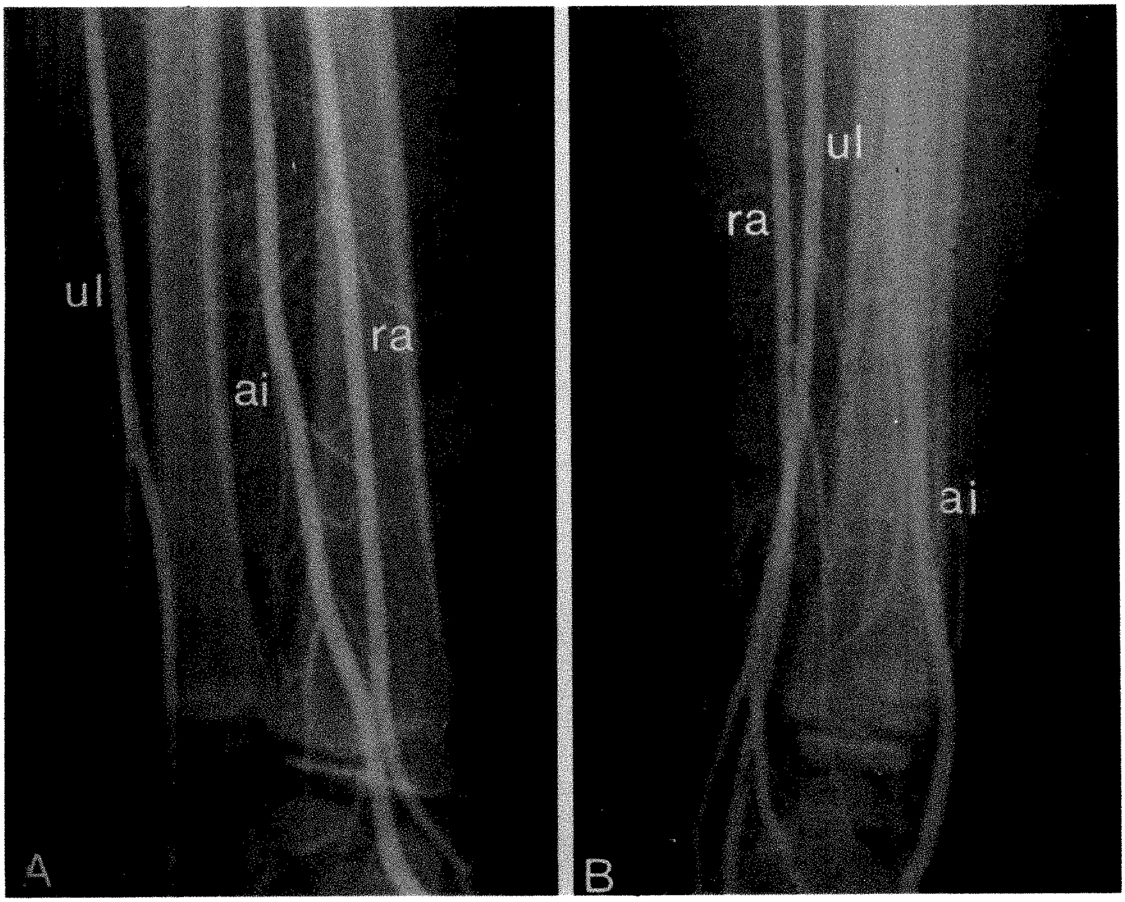

Fig. 3 *Anteroposterior (A) and lateral (B) view of patient with large anterior interosseous artery (ai) present together with the radial (ra) and ulnar (ul) arteries. The anterior interosseous artery appears on the back of the hand instead of the radial artery.*

seous artery, which runs down the flexor surface of the forearm and, when near the wrist, turns dorsally to appear over the back of the hand where it takes over the function of the radial artery (Fig. 3 (B)).

(3) Three patients had a weak radial artery pulsation in the normal position and a strong ulnar artery pulsation. Angiography in two confirmed a small radial and a relatively large ulnar artery (Fig. 4).

(4) In one patient the radial artery was absent and was not replaced with a dorsal artery. A brachial arteriogram showed a vestigial radial artery, which ends as fine muscular branches in the forearm (Fig. 5). The anterior interosseous artery was not hypertrophied.

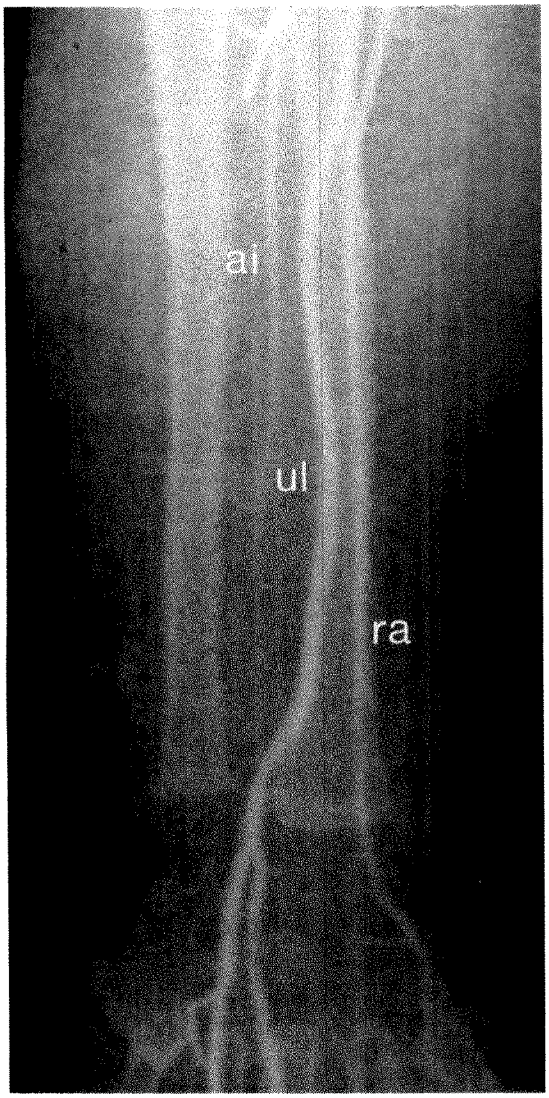

Fig. 4 *Small radial (ra) and large ulnar (ul) artery in one patient. Note rather lateral course of the ulnar artery in the forearm in this patient. ai=Anterior interosseous artery.*

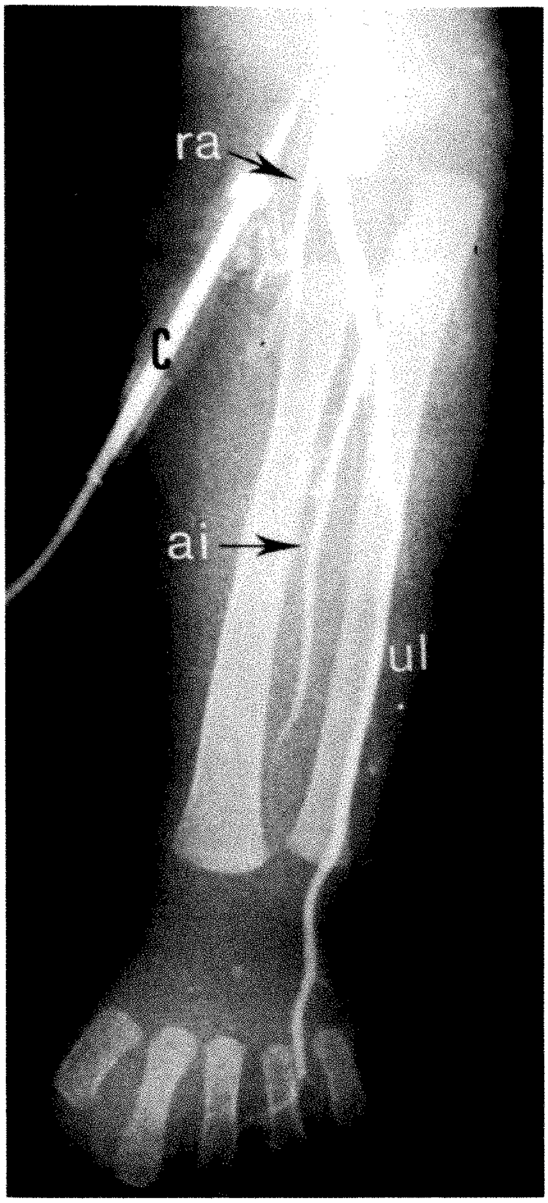

Fig. 5 *Forearm of patient with vestigial radial (ra) artery terminating in muscles of forearm. Normal ulnar (ul) and anterior interosseous (ai) artery. C=Cannula.*

The arterial abnormality was seen on both right and left hands in eight patients and was unilateral in four. When present on both sides the same type of abnormality was observed. There was no predilection for any particular type of congenital heart disease.

Discussion

Congenital heart disease is present in 40% (range 7–71%) of patients with Down's syndrome,[3 7 8] the commonest anomaly being an atrioventricular defect or ventricular septal defect. Abnormalities of the great vessels are uncommon. Coarctation of the aorta occurs in less than 1% of the congenital heart diseases seen in patients with Down's syndrome[4–6] compared with 5–8% in normal children.[7 8] An aberrant right subclavian artery originating from the descending aorta is probably more common in patients with Down's syndrome, with reported incidence varying from 2·5 to 37·5%, whereas it occurs in less than 10% of normal children with congenital heart disease and 0·5% of the general population.[9 10] This aberration was present in seven (14%) of our 50 patients with Down's syndrome with abnormal hearts. Other congenital vascular anomalies have not been reported. We were the first to describe abnormalities of the radial artery in Down's syndrome, being present in 18% of those patients with congenital heart disease and in 11% of those with normal hearts.

The radial artery normally originates from the brachial artery in the antecubital fossa and runs between the brachioradialis muscle and the flexor digitorum sublimis and flexor pollicis longus muscles up to the wrist where it becomes palpable between the tendon of the flexor carpi radialis muscle and the lateral prominence of the radius. Just beyond the styloid process of the radius it curves to the back of the hand over the lateral ligaments of the wrist joint and underneath the tendons of the abductor pollicis longus and extensor pollicis bravis muscles. It then passes between the heads of the first dorsal interosseous muscle into the palm to form the deep palmar arterial arch. Fowler, in his classic text on cardiac diagnosis, has mentioned that 'impairment of the radial pulse is commonly caused by an aberrant course of the artery so that it is deep and not readily palpated.'[11] A deep lying, non-palpable radial artery has also been suggested by other authors on clinical examination of the cardiovascular system.[12] Searching through the published reports on anatomy of the radial artery, however, yields no description of such an aberrant route of the radial artery in the forearm. The location of the ulnar artery pulsation in the wrist between the palmaris longus tendon and the pisiform bone is even more constant, and no deviation has been reported.

An abnormal course of the radial artery in the wrist running above instead of deep to the tendons of the abductor pollicis longus and extensor pollicis brevis on passing to the back of the hand has been described in five of 750 hands (0·7%) by McCormack.[13] Keen[18] found three among 284 hands (1%) in which the radial artery becomes superficial in the middle of the forearm, travelling across the surface of the brachioradialis muscle, and runs down in the superficial fascia to the wrist where it enters the first dorsal interosseous space in the usual manner. A superficial radial artery is also seen as a continuation of a 'superficial brachial artery', which takes its origin from the axillary artery or as the major branch of the brachial artery in the arm and travels superficially downwards. This superficial brachial and radial artery was present in 1·2% of McCormack's dissections.[13]

Eight of our patients had a superficial artery over the back of the wrist, but none of them seemed to bear the superficial or aberrant course of the radial artery described above. The dorsal artery seemed to emerge from beneath the extensor muscles in the distal forearm rather than across and over the brachioradialis muscle or the extensor tendons of the thumb. Angiographically, it seemed to be a direct continuation of the anterior interosseous artery, which travels between the radius and ulnar bones and then turns dorsally near the wrist to appear in the back of the hand. The radial artery was completely absent in seven and present in normal calibre in one patient. The anterior interosseous artery is indeed the most primitive axial vessel of the forearm and is the first to develop in the human embryo, in which it runs down the forearm and passes through the carpus to terminate on the dorsum of the hand.[15 19] This course of the vessel is still seen in the duck billed platypus (Ornithorhynchus). Thus it is reasonable to consider the abnormality seen in these patients as developmental absence of the radial artery and persistence of an embryologically dominant anterior interosseous artery, which in its distal portion takes over the function of the former.

Absence of the radial artery has hardly been reported. Charles and Chhatrapati have each described a case in which the lower end of the anterior interosseous artery took the course of radial at the wrist and into the hand as the deep palmar arterial arch.[14 15] Not a single case was found in a total of 1750 dissections of the hand carried out by McCormack, Coleman, and Motamed.[13 16 17] Our patient with vestigial radial artery resembles the case described by Chhatrapati, whose dissection showed the brachial artery divided into a larger branch, which was the ulnar artery, and a smaller branch, which was thin and short and ended in the substance of the brachioradialis muscle. Diminutive as the artery was in both cases, it should in fact represent a partially developed rather than absent radial artery.

Three of our patients showed a weak radial and a relatively strong ulnar artery pulsation, which was confirmed by a larger ulnar artery on angiography. A large radial artery in the human being is an evolutionary achievement in the development of the hand. In lower primates like the apes and gibbons, which are adept at climbing, supination and pronation of the hand are fairly free. The ulnar artery, being on the fixed side of the forearm, is the larger vessel, while the radial artery is generally smaller because constant rotatory movements of the radius will not facilitate flow through this vessel. In baboons, on the other hand, with their quadrupedal walking behaviour and less twisting movements of the wrist, the radial artery is larger than the ulnar. In the intermediate simian primates the two vessels are equal in size.[19]

The four types of abnormalities of the arteries in the forearm observed in our 12 patients seem to represent a range of developmental primitiveness in the formation of the arteries of the forearm in Down's syndrome. The anterior interosseous artery remains as the dominant vessel of the forearm when the radial artery fails to develop. In a single patient the anterior interosseous artery has persisted and shared codominance with the radial and ulnar arteries at the wrist. A vestigial or small radial artery compared with the ulnar artery represents an arrest at different stages of its development.

Patients with Down's syndrome are more likely to have congenital heart diseases requiring surgical correction. Arterial cannulation for monitoring of the blood pressure is commonplace during the perioperative period. An abnormal radial artery in the wrist should be carefully looked for and cannulation of this vessel or the ulnar artery should best be avoided less circulation to the hand be compromised.

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Effect of caffeine on pneumogram and apnoea of infancy

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SUMMARY We studied the efficacy of caffeine in improving pneumogram abnormalities and relieving clinically important apnoea of infancy in 23 infants. After obtaining a 12 hour pneumogram we administered caffeine citrate in a loading dose of 20 mg/kg followed by 5 mg/kg once daily. This dose achieved a trough caffeine blood concentration of 9·6 (SD 2·0) μg/ml. A repeat pneumogram performed seven to 10 days after the first pneumogram showed a significant reduction in the number of short and prolonged attacks of apnoea as well as in the per cent periodic breathing and apnoea density. Episodes of prolonged apnoea disappeared in all infants after administration of caffeine and in 11 infants all pneumogram abnormalities resolved. This improvement in the results of pneumograms was associated with resolution of clinically important apnoea requiring intervention. Caffeine was administered for 3·4 (SD 1·3) months and was well tolerated by all except two infants. We conclude that treatment with caffeine is helpful in preventing attacks of apnoea that require intervention, and improvement in the results of pneumograms after administration of caffeine predicts this favourable response.

Apnoea has been recognised as a major problem in many preterm and some full term infants before discharge from the nursery.[1 2] Evaluation in these infants usually fails to identify any underlying cause for the attacks of apnoea. Prolonged attacks of apnoea, especially in premature infants, are apparently not predictive of sudden infant death syndrome[1 3] but are often perceived by parents and physicians as a life threatening event with a risk of recurrence. Home monitoring has therefore been suggested in the management of these infants with unexplained apnoeic or cyanotic episodes.[4 5] In addition, treatment with theophylline has also been found to be an effective adjunct in the care of these infants.[6 7] Apnoea of prematurity can be treated with caffeine,[8] which has a wider safety margin than theophylline.[9] While the two abnormalities in the control of ventilation—that is, apnoea of prematurity and persistent infantile apnoea—may result from different mechanisms, we hypothesised that caffeine may be better suited for home use. As no systematic evaluation of caffeine has been performed in home circumstances we decided to evaluate the effect of home administration of caffeine on breathing patterns as measured by 12 hour pneumogram and on the incidence of clinically important apnoea.

Subjects and methods

We studied 19 preterm infants ready for discharge from the newborn nursery who were suffering from clinically important apnoea. We defined clinically important apnoea as a respiratory pause of at least 20 seconds in duration or less if accompanied by cyanosis or bradycardia.[4] We also studied four full term infants with clinically important apnoea, two of whom developed apnoea while they were still in the newborn nursery and two at home. Initial evaluation focused on the exclusion of the following medical conditions known to cause apnoea: infection, hypoglycaemia, hypocalcaemia, electrolyte imbalance, seizure disorder, gastro-oesophageal reflux, intracranial abnormalities, and congenital and chromosomal anomalies when appropriate. If an underlying cause for apnoea was identified appropriate treatment was begun. Infants with unexplained apnoea, requiring manual stimulation or bag and mask ventilation to terminate an episode of apnoea, were considered appropriate candidates for home monitoring and treatment with caffeine and formed the subjects for this study.

Caffeine was administered orally as caffeine citrate in a loading dose of 20 mg/kg followed by a maintenance dose of 5 mg/kg once daily. Maintenance caffeine was started 24 hours after the loading dose. We measured caffeine trough concentration in the blood (half to one hour before the dose) after five to seven days of treatment. Caffeine dosage was adjusted to maintain a blood concentration of 6–15 μg/ml.

We obtained 12 hour pneumogram recordings before and seven to 10 days after administration of caffeine. Subsequent pneumograms were obtained as clinically indicated. Pneumograms are two channel, slow speed recordings; one channel for electrocardiogram and one for respiratory pattern, as detected by thoracic impedance. The pre-caffeine pneumogram was performed in the hospital and the post-caffeine recording at home.

We used Medical Graphics Corporation (MGC) System 5000 to analyse the results of our pneumograms. The MGC Computer Assisted Pneumogram provides a scoring system, on a breath by breath basis, as a summary report and graphic display of apnoea, bradycardia, and periodic breathing. The computer system is capable of analysing the pneumogram in greater detail than is possible manually, and observer bias in analysis is eliminated. We visually checked the electrocardiogram and respiratory pattern tracing for artefacts and excluded all portions of the tracings with artefacts from analysis. As no control data for pneumogram analysis in premature infants using MGC System 5000 is available we also studied 15 infants with a birth weight of 1620 (SD 320) g and gestational age of 32·2 (SD 1·5) weeks at a postnatal age of 5·7 (SD 2·3) weeks, who were ready for discharge from the newborn nursery and had not had any attacks of apnoea.

We defined periodic breathing as three or more respiratory pauses of three seconds or longer interrupted by respiration for less than 20 seconds. The per cent periodic breathing was calculated by dividing the number of minutes of periodic breathing by the number of minutes of sleep time. We defined apnoea density as time spent in apnoea (duration of over six seconds) for each 100 minutes of sleep time.

All study infants were discharged home on cardiorespiratory monitors, which detect heart rate by the electrocardiographic signal and respiration by the impedance signal. The monitor has an alarm for attacks of apnoea as well as of bradycardia and tachycardia. In addition, the monitor has an audible beep and a flashing light to indicate the instantaneous heart rate and another light to indicate loose leads. We set the respiratory alarm to sound at 15 seconds of apnoea, the bradycardia alarm at heart rate less than two thirds of the baseline, and the tachycardia alarm at heart rate over 180 beats/min. All parents were given instruction in the use of the monitor and cardiopulmonary resuscitation. Parents were also instructed to maintain a diary of all alarms and interventions undertaken by them. We interviewed all parents in the neonatal follow up clinic to assess any complications related to the use of caffeine as well as the details of any attacks of apnoea or intervention reported by them.

Results are expressed as mean (SD). We used the Wilcoxon signed rank test to analyse the difference in the breathing pattern before and after administration of caffeine and the Wilcoxon rank sum test to compare control infants and infants with attacks of apnoea, which are distribution free methods (as the variables analysed are often not normally distributed). Categorical data were evaluated by χ^2 test. Results were considered significant if $p<0{\cdot}05$.

Results

Clinical characteristics of our study infants are shown in Table 1. Response to caffeine was similar in the two groups so the pneumogram results have been combined in Tables 2 and 3. Caffeine steady state blood concentration before the second pneumogram was 9·6 (2·0) μg/ml.

Total number of apnoeic episodes recorded on the 12 hour pneumogram performed before and after

Table 1 *Clinical characteristics of the study infants. Values are mean (SD)*

	Full term infants	*Preterm infants*	
		Controls	*With attacks of apnoea*
No	4	15	19
Birth weight (g)	2800 (430)	1620 (320)	1600 (600)
Gestational age (weeks)		32·2 (1·5)	32·0 (2·6)
Weight at first phonocardiogram (kg)	4·0 (2·4)	2·1 (1·2)	2·2 (1·1)
Postnatal age at first phonocardiogram (weeks)	2·0 (1·5)	5·7 (2·3)	5·0 (3·2)

Table 2 *No of apnoeic episodes in control group and infants with apnoea*

	Control group (n=15)	*Infants with apnoea (n=23)*	
		Before caffeine	*After caffeine*
Duration of attack of apnoea (secs):			
5–6	6 (5)	67 (54)	22 (31)*
7–10	1 (2)	34 (35)	9 (17)*
11–15	0	7 (19)	2 (7)
>15	0	8 (2)	0*
% Periodic breathing	0·3 (0·4)	4·4 (4·2)	1·2 (2·0)*
Apnoea density	0·1 (0·1)	1·0 (0·9)	0·3 (0·5)*

*Significant difference ($p<0·05$) in infants with apnoea in relation to treatment with caffeine.

administration of caffeine is shown in Table 2. Also contrasted in this Table are the pneumogram findings of normal premature infants before discharge from the newborn nursery. There was a significant difference between the control group and infants with attacks of apnoea before treatment with caffeine in all categories studied except for attacks of apnoea lasting 11–15 seconds. In infants with attacks of apnoea administration of caffeine was associated with a significant reduction in the total number of attacks in all categories analysed except for attacks lasting 11–15 seconds. Prolonged attacks (over 15 seconds in duration) or attacks associated with bradycardia were not seen after administration of caffeine. In addition, per cent periodic breathing and apnoea density were also significantly reduced. In comparison with the control group, infants with attacks of apnoea after administration of caffeine continued to have a significantly higher number of attacks in the 5–6 second category of apnoea. In all other categories of apnoea, per cent periodic breathing, and apnoea density, however, the control group was not significantly different from the group with attacks of apnoea after treatment with caffeine.

The number of infants with one or more attacks of apnoea before and after administration of caffeine as recorded on the pneumograms is shown in Table 3 Eleven infants became free of attacks of apnoea after administration of caffeine. Twelve infants continued to have short attacks, none of whom, however, had prolonged attacks (over 15 seconds in duration) or attacks associated with bradycardia. Also shown in Table 3 is the number of infants with periodic breathing in excess of 3·5% and apnoea density in excess of 1·5% in relation to treatment with caffeine. While these cut off values for excessive periodic breathing and apnoea density are not totally discriminative, infants with apnoea of infancy generally have values above and normal infants below these cut off values.[10, 11] The reduction in the number of infants with attacks of apnoea in all categories and excessive periodic breathing after adminsitration of caffeine is significant except for attacks lasting 11–15 seconds. The reduction in the number of infants with apnoea density over 1·5% in relation to administration of caffeine is not significant.

Home evaluation of our study infants showed that false alarms on the monitors were common. These alarms were related to loose leads and short episodes of bradycardia lasting less than 3–5 seconds (perhaps related to transient vagal stimulation). None of our study infants, however, had prolonged attacks of apnoea (over 15 seconds) or attacks associated with colour change or bradycardia requiring intervention (manual stimulation or mouth to mouth ventilation) while on caffeine. Two infants became irritable, restless, and jittery after starting treatment with caffeine. These symptoms resolved after stopping treatment with caffeine, and subsequently theophylline was well tolerated by them. Theophylline was administered to these infants one to two weeks after the second pneumogram and so did not affect the pneumogram analysis. The remaining 21 infants received caffeine for 3·4 (1·3) months. Seventeen infants had no obvious harmful effects related to caffeine. Four infants were judged by their parents to be somewhat more irritable and restless while on caffeine. Their daily activity, sleep,

Table 3 *No of infants with breathing pattern abnormalities before and after treatment with caffeine*

Breathing pattern	*Before caffeine*	*After caffeine*
No apnoea	0	11*
Duration of attack of apnoea (secs):		
5–6	21	11*
7–10	21	12*
11–15	7	2
>15	7	0*
% Periodic breathing		
>3·5	14	2*
% Apnoea density		
>1·5	8	3

*$p<0·05$.

and feeding patterns, however, were not altered. Caffeine blood concentrations did not correlate with symptoms and none of the infants had a blood concentration over 16 µg/ml.

Discussion

Most parents display anxiety at the prospect of caring for their infants who suffer from attacks of apnoea at home. Home monitoring is currently an accepted way of managing infants with attacks of apnoea. The ability of anxious parents to deal with an attack of apnoea detected by the monitor is, however, variable. Infants have been known to die of sudden infant death syndrome at home while being monitored.[12] Death at home in these monitored infants may be due either to the fact that sudden infant death syndrome is not preventable or to the inability of the parents to provide adequate resuscitation. Implicit in the home monitoring of infants with attacks of apnoea is the idea that parents can learn the skills of resuscitation and execute them when needed. To date this assumption is untested and unproven. It is important, therefore, to prevent prolonged attacks of apnoea at home that may require intervention.

Respirogenic properties of the methylxanthines, particularly caffeine, have been known for a long time. The exact site and mechanism of action, however, have not yet been clearly defined. Methylxanthines augment central inspiratory drive and increase chemoreceptor sensitivity to carbon dioxide.[9] Others factors that may facilitate this anti-apnoeic effect of methylxanthines include improved skeletal muscle contraction,[13] potentiation of catecholamine response,[14] improved metabolic homeostasis,[15] and improved oxygenation secondary to increased cardiac output, increased ventilation, and decreased hypoxic episodes.[16] Our results indicate that caffeine can be safely administered to most of these infants with attacks of apnoea. None of our infants developed clinically important apnoea requiring intervention while on caffeine. Thus our results are in agreement with Murat *et al*, who have shown caffeine to be efficacious in recurrent idiopathic apnoea of prematurity in the immediate neonatal period.[8] The long term harmful effects of caffeine, if any, are, however, unknown. It is prudent, therefore, not to use caffeine unnecessarily.

Pneumograms have been extensively used to evaluate infants at risk for sudden infant death syndrome. Recent data indicate that pneumogram findings are not very helpful in predicting the risk for sudden infant death syndrome.[3] Pneumogram findings may be quite helpful, however, in predicting the risk for prolonged sleep apnoea, Steinschneider has shown that infants with prolonged sleep apnoea have, during a single nap, more frequent and longer apnoeic pauses and more periodic attacks compared with normal infants.[17] Hunt *et al* have shown that home pneumograms can differentiate infants with prolonged attacks of apnoea from normal infants with 80% accuracy.[11] Our results indicate that improvement in pneumogram abnormalities with administration of caffeine is associated with resolution of prolonged attacks requiring intervention. Thus pneumogram abnormalities in conjunction with response to caffeine can be used to identify infants who are likely to benefit from administration of caffeine.

All of our study infants suffered from clinically important apnoea requiring intervention. Consequently, we were unable to control the environment in which our pneumograms were performed as this would have necessitated an additional seven to 10 days of admission to hospital. Our first pneumogram before administration of caffeine was performed in the hospital, while the second pneumogram after caffeine was performed at home. The effect of environmental changes on pneumogram findings is unknown. Our two measures of short attacks of apnoea, the per cent periodic breathing and apnoea density, should be similar as they are controlled by sleep time. Prolonged attacks of apnoea, on the other hand, may occur more often at home because of the quieter home environment. Our results are, however, contrary to this expectation and may be attributed to the administration of caffeine. Our results can also be criticised because we did not control for the maturational effect of the time interval of seven to 10 days between our first and second pneumogram. Sequential pneumogram changes have been studied by Richards *et al* and Hunt *et al.*[2] [11] These authors, however, studied only healthy full term infants at intervals of six weeks to three months, which makes comparison with our study difficult. Kelly *et al* have shown that repeat pneumograms after 5·7 (2·7) days in 11 infants, before treatment with a methylxanthine, did not result in resolution of excessive periodic breathing.[6] In addition, Hunt *et al* have shown a significant difference in pneumogram abnormalities between infants with attacks of apnoea studied at 7·7 (7·1) weeks compared with control infants at 1 and 3 months of age.[11] From these studies we conclude that infants with attacks of apnoea have persistent breathing pattern abnormalities that are not likely to resolve spontaneously within seven to 10 days. This conclusion is supported by the findings in two of our study infants who developed side effects from treatment with caffeine that necessitated stopping this drug after one week in one infant and two weeks in the other. Both of these infants had a recurrence of apnoea requiring intervention.

In conclusion, our data show that caffeine improves pneumogram abnormalities in infants suffering from attacks of apnoea. In addition, this improvement in pneumogram findings is associated with resolution of clinically important apnoea requiring intervention.

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Neonatal intestinal lactase activity

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SUMMARY The sequential changes in intestinal lactase activity of 40 neonates were measured indirectly from the differential uptake and excretion of lactose and the non-metabolisable disaccharide lactulose contained in formula feeds. A daily decline in urinary lactose:lactulose excretion ratios, reflecting a rise in intestinal lactase activity, followed formula feeding. Percentage decline was related directly to gestation: full term infants displayed a fivefold greater decline in lactosuria than infants with a gestation of 28 weeks during the first 10 days of milk feeding. The difference between lactose:lactulose ingestion and excretion ratios suggests that within five days of starting feeds intestinal hydrolysis of lactose exceeds 98% efficiency, even in very preterm infants.

Intestinal lactase activity is detectable in the fetal gut as early as eight weeks' gestation, occurring coincidentally with the previllous ridges.[1] Measurements of lactase activity from tissue obtained from aborted fetuses, stillbirths, and after unfed neonatal deaths have been reported.[2] Mucosal enzyme activities rise gradually between eight and 34 weeks' gestation and then more rapidly to term. Using indirect methods, a postnatal rise in lactase activity after beginning oral feeding in both preterm and full term newborn has been described.[3 4]

Such findings are reflected by the lactosuria observed during the neonatal period. A proportion of unhydrolysed lactose may be passively absorbed and excreted intact in the urine. Although the degree of lactosuria seems to be inversely related to gestational age at birth, and hence may mirror mucosal lactase activity,[5] the capacity of the neonatal gut to absorb disaccharide intact is also affected by its permeability characteristics.[6]

The use of the unmetabolisable reference disaccharide lactulose,[7] composed of fructose and galactose, offers a method of studying sequential changes in intestinal lactase activity as reflected by the quantity of lactose compared with lactulose occurring in the urine of infants fed milk containing these two enzymes. Both sugars have the same molecular weight (342 daltons) and size (0·52 nm) and share the same pathways of passive uptake. Less than 5% of oral loads of lactulose are absorbed in the newborn.[6 8]

The aim of this study was to follow the sequential change in intestinal lactase activity in a group of newborn infants being fed formula during the first 10 days of life, examining in particular its relation to postconceptional and postnatal ages.

Patients and methods

Forty newborn infants were studied for the first 10 days of life. All were patients of a single maternity hospital in Newcastle and received standard neonatal care throughout the study, which was performed with the informed consent of the parents and approval of the local ethical committee. The weights of the infants ranged from 760 to 4360 g and gestational ages from 27 to 42 weeks at birth.

All infants received an artificial milk formula containing 7 g lactose and 200 mg lactulose per 100 ml feed (lactose:lactulose ingestion ratio of 35:1). This lactulose content is well within that already present in several ready to feed formulas,[9] and no adverse effects were observed. Those babies whose oral feeding was delayed because of prematurity or respiratory disease received 10% dextrose intravenously until oral feeding began. Milk feeds were given by orogastric tube or bottle according to the infant's gestation and condition, but no baby's first feed was delayed longer than four days after birth. No infant suffered severe birth asphyxia. Seven infants required assisted ventilation for respiratory distress syndrome and 23 phototherapy for hyperbilirubinaemia.

A dual marker steady state method of study was used.[6 8] Infants received regular and continuous test feeds. After 24 hours, when a steady state of sugar input and output had been reached, a random urine sample was collected daily for the first two weeks of life from the preterm infants and until discharge from hospital from term infants. Urine samples were stored at −20°C with 0·1 ml sodium merthiolate until analysis. Such a method, using lactulose and mannitol as markers, has been validated in catheterised infants, in whom it was shown that a steady state of marker input and output is reached within five times the half life of each marker (20 hours).[8]

Disaccharide concentrations in urine specimens were assayed by gas-liquid chromatography, using turanose as an internal standard.[10] Trimethylsilylation of sugars was performed before chromatography to produce single derivatives of lactulose and turanose and α and β anomers of lactose. Concentrations were determined by comparison of the peak heights of test sugars with standards after summing the lactose peaks. Results were expressed as a urinary lactose:lactulose excretion ratio.

Multiple regression analysis was used to measure the trend in urinary lactose:lactulose excretion ratios after the start of feeding by fitting parallel trends for each infant and allowing for missing data. This method assumed that the plots for the ratios against days after starting feeds ran parallel. The effect of gestational age on the ratios was determined by linear regression for each day after starting feeds. The significance of this slope indicated whether or not the two were related and the magnitude of the slope the mean change in ratios for each extra week of gestation.

Results

Two hundred and twenty one urine specimens were collected from days 1–13 after starting feeds and analysed. The results for days 9–13 were combined to make sufficient numbers for analysis.

There was no significant relation between initial urinary lactose:lactulose excretion ratios and postconceptional age and weight. They ranged from 4·5 to 0·35 (mean 1·3), representing 7·7- to 100-fold differences from the ingestiuon ratio of 35.

The Figure shows the results broken down into three gestational groups—infants of 28, 34, and 40 weeks' gestation. The results are expressed as a percentage decline in urinary lactose:lactulose excretion ratios from initial values plotted against days after starting milk feeds. All three groups showed a decline in ratios during the first five days after the onset of milk feeds. Thereafter, the most mature infants (40 weeks' gestation) showed a continued fall in ratios (eightfold between days 1

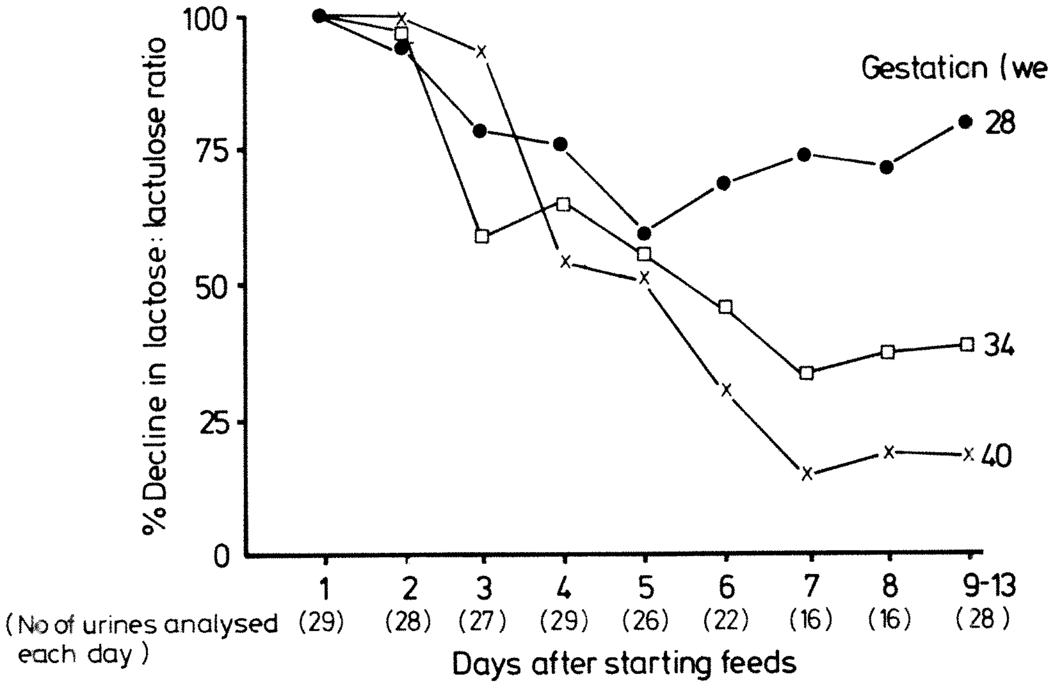

Figure *Percentage decline in urinary lactose:lactulose excretion ratios after milk feeding in infants of 28, 34, and 40 weeks' gestation at birth. There was a significant trend in ratios with gestational age from day 7 onwards (p≤0·01).*

and 7), and the most premature (28 weeks' gestation) none, with a persistence of appreciable lactosuria. Infants of 34 weeks' gestation showed a decline in lactose:lactulose ratios intermediate with their less and more mature colleagues. The difference between groups was significant from seven days onwards ($p<0{\cdot}01$).

Discussion

We have shown a rise in intestinal lactase activity after milk feeding in the newborn: the percentage increase is related directly to gestation, which is most pronounced in the term infant and least in the preterm infant.

It has been suggested that initial lactase activity is a function of postconceptional age.[2 13] Although our method does not allow the measurement of lactase activity before the onset of milk feeding, there was no significant relation between urinary lactose: lactulose excretion ratios and gestation immediately after the onset of milk feeding or during the five following days (Figure). Infants of all gestations showed a sequential rise in lactase activity during this period, and only thereafter was there a significant difference between gestational groups.

These findings contrast with those of Antonowicz and Lebenthal, who found a direct relation between unfed mucosal lactase activities and increasing gestation,[2] but accord with those of Boellner *et al*, who studied the lactose tolerance of preterm and term infants after feeding,[3] and Mayne *et al*, who studied the jejunal fluid sucrase:lactase ratios.[4]

Our findings suggest that the lactase activity of the newborn is equal to the immediate demands of milk feeding but that after five days, when the lactose load has risen appreciably, only the full term infant displays a complete capacity to use this sugar.

Human[13] and animal studies[14] have suggested that intestinal lactase activity is begun or stimulated by milk feeding. Within 24 hours of starting milk feeds all our infants displayed highly significant differences between lactose:lactulose excretion and ingestion ratios, indicating considerable hydrolysis of lactose during this time. On the first day after starting oral feeds the mean excretion:ingestion ratio was 0·04 (1·3:35) and within five days had dropped further to 0·02 (0·7:35) ($p<0{\cdot}0001$ in both instances), suggesting hydrolysis of 98% of ingested lactose. These conclusions contrast with those obtained using breath hydrogen measurements alone to assess lactose utilisation, which suggest significant malabsorption of lactose in preterm[15] and term infants.[16] They conform, however, to the recent finding, using [13C] labelled lactose, that lactose absorption in the small intestine is nearly complete in the full term infant fed formula.[17] In clinical practice lactose utilisation is not regarded as a major practical constraint to the growth of the newborn, and the indirect measurements of unhydrolysed lactose described both here and in [13C] studies may simply signify the more than adequate amounts of lactose ingested by the newborn.

It is not possible, using this method, to show whether such changes are the direct effect of milk feeding. Analysis of our results by postnatal age simply moves the values for the most preterm infants (as shown in the Figure) to the right. To answer this question it would be necessary to study infants denied milk feeding and those receiving a non-lactose containing formula.

Our findings reflect the degree of maturation of mucosal function of infants of different gestational ages and the capacity of the neonatal intestinal epithelium to respond to the demands of enteral nutrition. They accord with those previously reported describing the maturation in intestinal permeability to lactulose that follows feeding in the newborn.[6] Preterm infants of less than 34 weeks' gestation exhibited a higher intestinal permeability than those more mature at birth, and all showed an appreciable decline in lactulose uptake during the first week of milk feeding.

The effect of such changes in permeability on the uptake of intact lactose is eliminated by the comparison of its uptake with that of the non-metabolisable reference marker lactulose. Both are handled by the body in the same ways, from ingestion to excretion, except for their differing susceptibility to hydrolysis by lactase. Both disaccharides traverse the intestinal wall by simple passive diffusion and share equal volumes of distribution and rates of renal clearance.[11 12 18]

It is unlikely that selective breakdown of lactose by micro-organisms in the gastrointestinal tract accounts for our findings. Colonisation of the healthy neonatal small bowel, the site of passive disaccharide absorption, is negligible,[19] and on reaching the large bowel both disaccharides are equally subject to breakdown by bacterial flora.[16 17 20]

The dual marker steady state method offers a simple, convenient, non-invasive way of studying sequential changes in intestinal lactase acitivity in infant fed formula. Our findings suggest mucosal lactose hydrolysis approaches optimal efficiency soon after the onset of milk feeding, even in the very preterm infant, which displays a persisting lactosuria representing no more than the 2% of lactose that escapes hydrolysis in the small intestine.

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Short reports

Neuropathy in a petrol sniffer

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SUMMARY A 4 year old boy developed a profound motor neuropathy after repeated deliberate inhalation of petroleum vapour. The condition was characterised by extreme slowing of the nerve conduction velocity. He made a gradual recovery over six months. The neuropathy was attributed to the N-hexane component of petroleum.

The deliberate sniffing of petrol (gasoline) to produce euphoria is known to cause acute neurological dysfunction, but chronic complications of this practice are rarely reported. The case described here is remarkable both for the youthfulness of the sniffer and for the pattern of neurological damage.

Case report

The patient was a Sudanese boy living in Khartoum. His family history and previous health were unremarkable.

At age 4 years 1 month a disturbance of gait and balance were noted but the symptoms were mild and initially ignored. His mother observed that he sometimes smelt of petrol. At age 4 years 4 months he was found comatose beside an open can of petrol that was stored in an outbuilding. Dyspnoea, hypoxia, and signs of encephalopathy persisted for 48 hours. When he recovered he was profoundly weak, hypotonic, and unable to stand or walk, but intellect, speech, and social behaviour were unimpaired.

Table *Results of investigations of motor nerve conduction*

Nerve	*Distal latency (millisecs)*	*Conduction velocity (m/sec)*	*Amplitude (uv)*
Right medial popliteal, knee-ankle	49·7	0·5	50
Right lateral popliteal	38·4	0·5	50
Right median, elbow-wrist	14·6	0·5	450
Right ulnar, elbow-wrist	10·2	0·5	100

Two months later, when he was seen in London, he could sit but was unable to stand. There was mild symmetrical weakness of the facial muscles and of all limbs. The legs were more affected than the arms. All four limbs were hypotonic and areflexic with some muscle wasting.

No sensory or cerebellar signs could be shown. The features were those of a predominantly motor neuropathy.

Investigations. Immediately after the acute episode, a blood lead concentration measured in Sudan was 2·1 μmol/l.

Two months later the following investigations were normal: blood count and film, erythrocyte sedimentation rate, urea, sodium, potassium, calcium, phosphate, and random glucose concentrations, liver function tests, urine reducing substances, creatine kinase activity, urinalysis, *x* ray films of skull, chest, and legs, blood lead concentration (0.5 μmol/l; normal = <1·8), visual acuity, visual evoked responses, audiogram.

The only abnormal investigation was the motor nerve conduction velocity (see Table).

Progress. When last seen, seven months after the acute illness, he could walk and there was only minimal weakness.

Discussion

The acute effects of petrol inhalation are those of an encephalopathy with euphoria, lethargy, anorexia, speech disturbances, blurred vision, and seizures.[1] Sniffing is primarily an activity of teenagers, though in communities where the practice is widespread 7 and 8 year olds may become involved.[2] It is most unusual for a 4 year old to discover and indulge the habit in isolation.

The alkyl leads (commonly tetraethyl lead and tetramethyl lead in the United Kingdom) and triorthocresyl phosphate along with lead scavengers are added to petroleum as anti-knock agents. These, along with the hexane isomers, are usually assumed to be the main toxic constituents of gasoline. The alkyl leads can be absorbed by inhalation but triorthocresyl phosphate is less volatile. The composition of the gasoline that the child was exposed to in Sudan is not known.

Lead poisoning is more likely to cause a mononeuropathy and the nerve conduction is only slightly reduced. In our patient, however, there was gross slowing of the conduction velocity. Furthermore, lead concentrations, *x* ray films, and the blood picture was normal. Karani[3] reported a case of toxic neuropathy in a young man who regularly drank petrol and attributed this to the additive triorthocresyl phosphate,[3] but this substance is unlikely to be absorbed in large quantities by sniffing petrol vapour.

We suggest that the profound motor neuropathy in our patient was probably caused by the N-hexane component of petroleum.[4] There are many reports of a similar neuropathy occurring in glue sniffers and in workers exposed to industrial sources of N-hexane or petroleum benzine. N-hexane seems to be the main toxic agent in organic solvent mixtures; toluene and other hydrocarbons, though potentially neurotoxic, seem to exert some protective effect against the nerve damage caused by N-hexane. The clinical features depend to some extent on the length and level of exposure. A motor neuropathy is usually the predominant finding, though in some cases there are also some sensory symptoms. Deterioration often continues after exposure has ceased. The motor nerve conduction velocity typically is grossly reduced and histological examination reveals a primary axonal neuropathy with secondary effects on the myelin and pronounced nodal widening.[5]

We thank Professor H Lambert for referring the patient and Professor R Anderson for helpful advice.

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Hypovitaminosis E induced neuropathy in exocrine pancreatic failure

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SUMMARY A 4 year old girl with congenital nerve deafness and pancreatic insufficiency had incapacitating ataxia. Electrophysiological studies of the median nerve and the brain stem evoked response were abnormal. Serum vitamin E concentration was low. After intramuscular injections of vitamin E the ataxia disappeared and electrophysiological variables reverted to normal.

This report describes a 4 year old girl with a variant of the pancreatic deficiency and congenital nerve deafness syndrome. As a consequence of the accompanying malabsorption she had hypovitaminosis E, incapacitating ataxia, and abnormal electrophysiological studies of the nervous system. Treatment with intramuscular vitamin E resulted in clinical and functional improvement.

Case report

The patient was a 4 year old girl, the oldest of three sisters born to non-consanguineous Arab parents. Her birth weight was 2700 g. At the age of 1 year she was noticed to be suffering from abdominal distension, frequent loose smelly stools, and failure to gain weight in spite of a ravenous appetite. Early in life she had been found to have impaired hearing, with a resultant delay in speech development. At 13 months an audiogram showed bilateral severe sensorineural hearing loss. Her motor development was delayed: she could sit and crawl at 1 year, stand by 2, and walk at 2½.

On admission her weight was 11 kg, height 85 cm, and head circumference 47 cm (50th centile for 15, 18, and 21 months, respectively). She stood on a wide base and had a grossly unsteady gait and a coarse tremor of her hands. Her tendon reflexes were absent. Routine laboratory investigations yielded normal results. Her serum IgA concentration was raised. Vitamin E concentrations were 0–0·1 mg/100ml (normal 0·5–1·5 mg/100ml) and no rise could be obtained after oral administration of vitamin E in a dose of 100 mg/kg/day. Serum cholesterol was 54 mg/100ml and the three day stool collection showed an excretion of 21·7 g fat/day. The sweat test yielded normal results.

A small intestinal biopsy produced normal results by light microscopy. The chest *x* ray yielded normal results, the wrist *x* rays showed a bone age compatible with a chronological age of 1·5 years, and there was no evidence of rickets. A barium meal, endoscopic retrograde choledochopancreatography and ultrasonography of the pancreas yielded normal results.

Pancreation function was estimated by duodenal intubation and subsequent intravenous injection of cholecystokinin octapeptide (Kinevac, Squibb Co, New Brunswick, New Jersey, United States). Only small volumes of duodenal juice were obtained after stimulation with cholecystokinin octapeptide, and pH rose to 6·7. Trypsin remained absent and only minute amounts of lipase and amylase activities could be detected ('Phadebas amylase test', Pharmacia diagnostics, Uppsala, Sweden).

The electrophysiological studies of brain stem and peripheral nerves are presented in the Table. A biopsy examination of the sural nerve yielded normal results.

Table 1 *Electrophysiological studies of the median nerve and brain stem auditory evoked response*

	Before treatment	*After treatment*	*Normal*
Median nerve			
Distal latency (msec)	6·2	3·9	<3·6
Amplitude (mv)	4	6·1	>5
Conduction velocity (msec)	17·8	35·2	>32
F response latency (msec)	31	27	<28
Brain stem auditory evoked response			
Latency (msec):			
Wave 1	2·1	1·6	<1·6
Wave 3	3·9	3·5	<3·4
Wave 5	7·3	6	<6·1
Brain stem transmission time (msec)	5·2	4·4	≤4·4
Amplitude of wave V (mv)	0·2	4·1	

A diagnosis of pancreatic insufficiency was made and treatment with pancreatic enzyme supplements (Viokase^R, AH Robbins, Monticello, Illinois, United States) was begun. Within one month she gained 2·5 kg in weight. Daily intramuscular injections of 100 mg vitamin E (Evitol, Hoffman La Roche, Basel) were given for 14 days.

After two months her gait became steady, the tremor disappeared, the deep reflexes returned, and her behaviour became sociable. Her serum vitamin E concentration rose to 1·7 mg/100 ml, and the pronounced improvement in the electrophysiological studies is shown in the Table.

Discussion

Our patient suffered from exocrine pancreatic insufficiency and a sensory-neural defect of hearing. This combination of clinical features has been described previously by several authors.[1 2] Our patient differed from them in that other features of this syndrome were not found. Cystic fibrosis was excluded by a normal sweat test and Schwachman's syndrome by normal skeletal *x* rays and blood picture.

Clinically, the most important feature of our patient was the early onset of tremor, ataxia, and absent tendon reflexes, presumably due to hypovitaminosis E. In pancreatic insufficiency low vitamin E concentrations can be found in early childhood,[3] but neurological signs have not, so far, been found before the age of 10 years.[4] Large oral doses of vitamin E, of the order of 100 mg/kg, are usually capable of restoring normal body stores of this vitamin. Our patient did not respond to oral treatment but required intramuscular treatment.

Electrophysiological studies have been reported by a number of authors, some of whom noticed improvement after treatment with vitamin E.[5 6] With this treatment there was not only pronounced and rapid clinical improvement, but we could show reversion to normal or near normal values of her median nerve distal latency, amplitude, conduction velocity, and brain stem evoked responses.

This case shows that in pancreatic insufficiency lack of vitamin E with its associated nervous damage may occur early in life. The implications for children with cystic fibrosis are obvious. While borderline or low concentrations of vitamin E are often found in cystic fibrosis, tremor, weakness, and absent tendon reflexes may be wrongly ascribed to the basic disease and malnutrition rather than to vitamin E deficiency. Electrophysiological studies such as were performed in this patient may help to diagnose the effects of vitamin E induced neurologic dysfunction. In addition, electrophysiological studies may be a good variable to measure the effects of treatment.

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Recurrent sepsis and gastrointestinal ulceration due to child abuse

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SUMMARY An 11 year old girl developed progressive upper gastrointestinal ulceration and recurrent episodes of intravenous catheter associated polymicrobial septicaemia. Evaluation failed to establish a cause. After exclusion of the parents and careful surveillance of the patient she improved, supporting the diagnosis of suspected child abuse (a form of Meadow's syndrome).

Meadow's syndrome (Munchausen's syndrome by proxy) is a form of child abuse in which a parent feigns illness in his or her child.[1] In a variant form the parent actually induces illness in the child. The diagnosis is confirmed by surreptitious observations,[2] confrontation of the parents and admission of guilt,[3] and/or selected laboratory tests.[4] This paper reports a girl with recurrent septicaemia and gastrointestinal ulceration of unknown aetiology who progressively deteriorated over a period of one year. She improved after exclusion of her parents and constant surveillance.

Case report

An 11 year old girl weighing 39 kg developed fever, cough, and protracted vomiting in January 1983, two months after a gastric ulcer had been diagnosed in her 14 year old brother. During a five week admission to hospital she had persistent vomiting and intermittent diarrhoea. She was transferred to Schneider Children's Hospital where examination revealed a thin, mildly dehydrated child weighing 33·8 kg who was otherwise normal.

Laboratory evaluation showed a haemoglobin concentration of 12·6 g/dl and serum protein concentration of 5·9 g/100ml. The following tests yielded normal or negative results: leucocyte count and differential, erythrocyte sedimentation rate, serum albumin, serum electrolyte, and immunoglobulin concentrations, urinalysis, stool culture, three stool examinations for ova and parasites, chest radiography, and barium contrast studies of the upper and lower gastrointestinal tracts, including views of the terminal ileum. Upper gastrointestinal endoscopy revealed a solitary lesser curve gastric ulcer. Cimetidine and antacids were administered with satisfactory clinical response.

Five days after discharge she developed a recurrence of abdominal pain and intractable vomiting and complained of a sore throat. On re-admission physical examination was remarkable for an erythematous pharynx and a tongue ulcer. Repeat endoscopic examination 20 days after the first revealed persistence of the gastric ulcer and a new deep 2 cm ulcer of the distal oesophagus. Serum amylase and gastrin activities were normal as was a secretin stimulation study. Sucralfate was added to the regimen and the cimetidine increased. After discharge episodes of vomiting and abdominal pain recurred and in May 1983 a mid-oesophageal stricture was documented. Oesophageal dilatation was performed but continued dysphagia necessitated a fundoplication and gastrostomy in June. Abdominal exploration at that time revealed no evidence of inflammatory disease involving the small or large bowel. Liver, gall bladder, biliary tree, and pancreas were normal. In September 1983 the patient developed severe abdominal pain and intolerance to feedings after she was given an antibiotic (ampicillin) through the gastrostomy tube. Endoscopic examination revealed multiple ulcerations of the gastric antrum, immediately distal to the gastrostomy tube site. Subsequently, feeding intolerance recurred, requiring re-admission for treatment of dehydration on two occasions during the next two months.

During the patient's admission to hospital in May 1983 after diagnosis of the oesophageal stricture, total parenteral nutrition was begun through a centrally placed catheter. There was an acute onset of fever associated with visible particulate material in the alimentation bottle. Blood culture yielded negative results, but fluid from the bottle grew *Candida albicans*, *Staphylococcus epidermidis*, and *Streptococcus viridans*. Culture of hyperalimentation fluid (routinely performed by the hospital pharmacy before dispensing of the fluid) yielded negative results. Furthermore, no other patients with abnormal or infected hyperalimentation fluid were noted at the time.

Over the next six months there was a recurrent pattern of abrupt fever associated with bacteraemia; all these episodes occurred at a time when an intravascular catheter was in place. She had 39 positive blood cultures over eight months, which grew two fungal and at least 15 different bacterial species. They were often polymicrobial (12 blood cultures), caused by micro-organisms that are unusual in catheter associated bacteraemia—for example, *Veillonella parvula*—and often due to organisms that are normal oral or faecal flora. Furthermore, these episodes were often associated with purulent drainage and phlebitis at the catheter site, and there was a prompt response when specific antimicrobial treatment was combined with removal of the catheter. Immunologic evaluation repeatedly showed normal numbers of polymorphonuclear leucocytes, lymphocytes, and monocytes. A nitro blue tetrazolium test, and tests of immunoglobulins, complement (C3, C4, and CH50), and cellular immunity yielded normal results. A gallium scan, computed tomograms of head and abdomen, and multiple echocardiograms as well as abdominal exploration and thoractomy with mediastinal and oesophageal exploration failed to reveal any abscess, focus of infection, or source for continuous seeding of the bloodstream.

Throughout the patient's multiple and prolonged admissions to hospital the mother was constantly at the bedside. Rather than appearing discouraged by her daughter's continued deterioration, she provided the nursing and medical staff with constant encouragement. She applauded the staff for their efforts and assured them they were doing everything possible. Though the parents were encouraged to seek evaluation at another tertiary care centre for further opinion and management, they returned to Schneider Children's Hospital, where the mother and the child felt 'more comfortable'. In October 1983 the mother was confronted with the suspicion that she was instrumental in the production of the bacteraemias. Her response was 'I can see how you might think that', but she denied contaminating the indwelling catheters.

The final admission of the child to our hospital was in late December 1983. Several days after transfer, abdominal exploration revealed a perforated jejunum (after passage of a transpyloric feeding tube at the local hospital). Careful abdominal exploration during laparotomy showed no evidence of chronic inflammatory bowel disease. One week later she developed high fever, became hypotensive, and was critically ill. Multiple blood cultures became positive for *Candida albicans*, and amphotericin B was administered. She improved, but 10 days later *Streptococcus faecalis* bacteraemia was associated with thrombosis and infection at a femoral catheter site. Chest pain and pulmonary infiltrates developed and lung scan findings were consistent with the clinical diagnosis of a septic pulmonary embolus.

At this point (February 1984) the parents were prohibited from visiting the patient, and she was placed under constant observation (a nurse's aide was always at the bedside). A Broviac catheter was placed. Her body weight was 27·2 kg. She subsequently showed slow but progressive improvement. Her Broviac catheter was electively removed eight weeks later. (This was the first of eight central venous catheters to be electively removed.) She tolerated alimentation by gastrostomy tube and began to drink and eat. She was afebrile from mid-February to the day of discharge (25 April). She was discharged to foster care weighing 36·7 kg after a total of 24 hospital admissions and 375 hospital days.

She has since returned to school and has not required admission to a hospital in the 15 months since discharge. Her weight is 40·8 kg. The judge's ruling after a protracted trial in family court found the parents guilty of child abuse, and the child remains in foster care.

Discussion

This child's gastrointestinal illness and bouts of recurrent infections continued for more than a year before her physicians' clinical impression that her illness was induced was strong enough to exclude her parents. The basis for suspecting that her infections were exogenously induced included: (1) Virtually all her infections were catheter associated; they were often polymicrobial or associated with organisms not usually associated with catheter associated sepsis. (2) Despite extensive radiologic investigations and surgical exploration (of abdomen and chest), no focus of infection or source for bloodstream seeding was identified. (3) A host defence problem was unlikely because extensive immunologic evaluation did not reveal appreciable abnormalities and the patient responded promptly to treatment and did not develop infections at sites commonly infected in patients with immunodeficiency (paranasal sinus, oral mucosa, lung, gastrointestinal tract, and skin other than catheter sites).

Similarly, the gastrointestinal ulceration remained inexplicable, with progressive ulceration while under optimal medical management. Multiple endoscopic procedures, blood tests, biopsy examinations and surgical explorations failed to find a cause. During admission to hospital there was one instance in which the mother reported bleeding from the gastrostomy tube, yet the red liquid recovered was guaiac negative. On another occasion, aspirin was detected in the blood, although it was never prescribed. Ingestion of a caustic substance or substances could have accounted for the gastrointestinal complaints as well as the endoscopic findings.

A pattern was discernable where the patient developed an exacerbation of gastrointestinal disease (often associated with new sites of ulceration) while at home and developed fever with bacteraemia in the hospital while an intravenous catheter was in place. The strongest evidence of exogenously induced illness was her remarkable recovery after exclusion of her parents and her good health during the 15 months since discharge while in foster care.

The patient's mother was probably responsible for inducing her illness. Her mother was at her bedside 24 hours a day during weekdays and seemed to be caring and attentive, features previously described in these mothers.[5] She had a bland affect, avoided eye contact when conversing, was obese, and was noted by a consultant psychiatrist to be slightly depressed. Although she was not employed in the medical field, she showed medical sophistication. Contrary to the experience of Meadow,[5] however, confrontation of this mother did not result in stopping of her child's infections and gastrointestinal symptoms. As our patient was often admitted from home with symptoms and had infections at three different hospitals it is inconceivable that medical personnel were involved in inducing her infections. Finally, we do not believe that the patient was responsible for inducing her own symptoms (Munchausen's syndrome). The patient was once heard asking her mother why she was fiddling with her intravenous line and when told of our suspicions she was incredulous. On one occasion, in which she developed a polymicrobial sepsis with infection at the catheter site, she could not have tampered with the catheter or tubing because she had spent the previous 24 hours with both hands restrained—one for the intravenous catheter and the other completely covered by a dressing for treatment of a previous thrombophlebitis. The child was interviewed on several occasions by a psychiatrist, social workers, and her primary physicians, but these discussions did not yield helpful information regarding the induction of her gastrointestinal illness or infections.

The severity of the symptoms prompted multiple invasive medical procedures. As without excluding the parents this child may have died[1] [5] it is critically important to consider the diagnosis of Meadow's syndrome in any child with inexplicable symptoms and signs, including recurrent episodes of polymicrobial septicaemia.[3] [4] Physicians must be cognisant of the increasing complexity of the presenting features of such cases as the presentation with both gastrointestinal disease and recurrent septicaemias led to delay in diagnosis. Among some of the physicians intimately involved in her care, there was disbelief and scepticism when legal measures were begun to exclude the parents. In the absence of an admission of guilt or clear cut proof of culpability a diagnostic (and therapeutic) trial of exclusion of the parent(s) may be necessary when this diagnosis is suspected.

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Familial persistent ductus arteriosus

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SUMMARY The occurrence of isolated persistent ductus arteriosus in three generations of one family with surgical correction is described. The high incidence of the malformation in this family suggests autosomal dominant inheritance rather than a polygenic mode of inheritance.

It is generally accepted that the inherited contribution to most forms of congenital heart disease has a polygenic mode of transmission. The familial occurrence of persistent ductus arteriosus is well recognised. Two large surveys of relatives of patients with persistent ductus arteriosus showed a low recurrence rate of between 1 and 2·5% in the subsequent generation.[1, 2] Case reports on individual families, however, have shown a much higher recurrence rate, and while this might represent case clustering with a polygenic inheritance, different forms of inheritance probably occur in these families.

Documented reports of persistent ductus arteriosus in three generations are rare;[3] this report details a family with a high incidence of persistent ductus arteriosus, involving three generations in the absence of consanguinity. The early generations of this family were previously reported by Burman.[4]

Case reports

Two siblings presented to our unit with isolated persistent ductus arteriosus, and the strong family history obtained led to an investigation of the family's medical records. The Figure shows the pedigree of this family. The two affected children (IV_1 and IV_2) are the only children of the non-consanguineous marriage of III_6 and III_7. The girl (IV_1) presented at 3 years with an asymptomatic cardiac murmur. There was a high volume pulse and the typical continuous murmur of a persistent ductus arteriosus. Echocardiography and cardiac catheterisation confirmed the presence of isolated persistent ductus arteriosus with a pulmonary artery pressure of 24/10 mm Hg (mean pressure 13 mm Hg). The persistent ductus arteriosus was ligated and divided, and the girl remains asymptomatic with no cardiac murmurs.

The boy (IV_2) presented at 4 months with failure to thrive, vomiting, and breathlessness during feeding. Examination revealed a collapsing pulse with clinical evidence of left ventricular hypertrophy. There was a harsh, long, grade 4/6 systolic murmur audible at the left sternal edge and pulmonary area with no diastolic murmur. A loud third heart sound was present with accentuation of the pulmonary component of the second sound. Investigation showed isolated persistent ductus arteriosus with a large left to right shunt and pulmonary hypertension. The pulmonary artery pressure was 50/22 (mean 30) mm Hg compared with an aortic pressure of 90/25 (mean 44) mm Hg. At the age of 6 months ligation and division of a short wide persistent ductus arteriosus was performed. He is now asymptomatic with a quiet pulmonary ejection murmur.

The mother (III_6) of these children is 25 years old and presented in infancy with cardiac failure associated with a persistent ductus arteriosus. Ligation of the ductus was performed at 1 year and she is now asymptomatic and normal on examination. She is the only child resulting from the non-consanguineous marriage of II_5 and II_6. Her father (II_5) had isolated persistent ductus arteriosus with appreciable pulmonary hypertension confirmed by cardiac catheterisation. In 1957, at the age of 28 years,

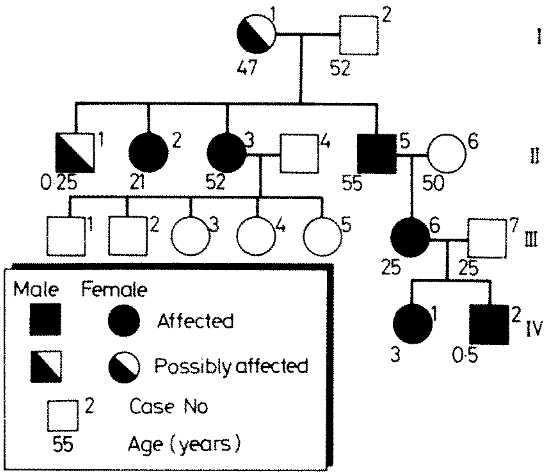

Figure *Family history of two siblings who presented with isolated patent ductus arteriosus.*

ligation of the ductus was performed and he lived until 1984 when he died of a non-cardiac cause.

He (II_5) had three siblings and both his sisters (II_2 and II_3) had surgically proved persistent ductus arteriosus. The first sister (II_2) had a persistent ductus arteriosus ligated in 1954 at 21 years. She died in the early postoperative period and it was considered on clinical grounds that she had established pulmonary vascular disease. The other sister (II_3) had a persistent ductus arteriosus diagnosed at the age of 24 and ductal ligation was performed in 1957. She is alive and well with five unaffected children. The other sibling (II_1) died during the early 1930s when 3 months old. The certified cause of death was acute bronchitis and marasmus. No cardiac abnormality was diagnosed.

There are no known cases of persistent ductus arteriosus in previous generations. The great grandfather (I_2) died at the age of 52 from pneumonia. The great grandmother (I_1) died at the age of 47 from cardiac failure. She presented in atrial fibrillation with peripheral and pulmonary oedema. No murmurs were documented, but a mitral valve lesion was suspected. Chest *x* ray showed considerable cardiomegaly with unusual 'right atrial enlargement'. No autopsy information is available. It is possible that her cardiac condition was due to Eisenmenger's syndrome related to a persistent ductus arteriosus.

Discussion

Persistent ductus arteriosus is a heterogenous condition. It may occur in association with complex congenital heart disease, with multiple abnormalities in other systems, or as an isolated defect. Environmental factors play a role in its pathogenesis—for example, in the maternal rubella syndrome or hypoxia (high altitude or neonatal respiratory distress syndrome)—and a genetic contribution is well recognised.

Large surveys of patients with a persistent ductus arteriosus show a low recurrence rate in siblings and children with a female predominance[1 2] consistent with a polygenic mode of inheritance. Animal studies have supported the hypothesis of polygenic inheritance.[5] A number of case reports have documented families where the incidence of persistent ductus arteriosus is higher than might be expected with a polygenic mode of inheritance. Most reports have concerned normal parents with multiple affected siblings,[6] and while this might represent case clustering with polygenic inheritance, it is possible that autosomal recessive inheritance is operating. The family in this report has well documented cases of isolated persistent ductus arteriosus with high frequency in three generations. Both males and females are affected in the absence of consanguinity. This pattern of inheritance is highly suggestive of autosomal dominant inheritance and is less likely to occur with polygenic inheritance.

This pattern of inheritance is uncommon as no similar families have been reported from this country. Burman's report concerned the same family when persistent ductus arteriosus was documented in two generations.[4]

Thus, while most cases of persistent ductus arteriosus seem to be multifactoral in origin with polygenic heredity influences interacting with environmental factors, a subgroup of patients exist with a much stronger genetic component. The recognition of such subgroups has obvious importance for the counselling of the couples concerned regarding risks of recurrence and in the wider context reminds us that what seems to be a single anatomical lesion is actually a heterogenous condition with diverse environmental and genetic causes.

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Prolonged positive airway pressure for severe neonatal tracheobronchomalacia

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SUMMARY A very low birthweight preterm baby with respiratory distress at birth was found to have severe congenital tracheobronchomalacia. Continuous positive airway pressure was given through an endotracheal tube without tracheostomy for 15 weeks before unassisted respiration could be maintained. Diagnosis was made and progress monitored by laryngobronchoscopy on three occasions.

Disorders of the large airways in the newborn are uncommon and the signs may be attributed to pulmonary disease, particularly in preterm babies. This case of a baby with severe congenital tracheobronchomalacia illustrates the difficulties in making the diagnosis in a very low birthweight infant and the long term support of ventilation necessary for a successful outcome.

Case report

A boy was born by emergency caesarean section weighing 1060 g after prolapse of the umbilical cord at 27 weeks' gestation. The parents were white and unrelated. The pregnancy had been otherwise normal.

At birth he cried and established spontaneous regular breathing but before 1 minute of age developed intercostal and sternal recession and became cyanosed. He was resuscitated with endotracheal intubation and positive pressure ventilation with rapid improvement. Artificial ventilation was continued until admission to the intensive care nursery when his temperature was 36·0°C, blood glucose concentration 5·0 mmol/l (90 mg/100 ml), and packed cell volume 40%. Signs of respiratory distress persisted. Examination showed a normal preterm male infant without any obvious malformations or dysmorphic features. An umbilical arterial catheter was inserted, a full infection screen carried out, and treatment with antibiotics started. Chest radiographs showed no signs of hyaline membrane disease or other pulmonary disease. The lecithin: sphingomyelin ratio measured in pharyngeal secretions aspirated at 2 hours of age was 3·6 (normal >1·8). Artificial ventilation could be rapidly decreased to six breaths per minute with a fractional inspiratory oxygen of 0·23. Initial bacterial cultures were negative. Continuous positive airway pressure was then applied but an attack of apnoea occurred and treatment with aminophylline was begun on the fourth day. On the seventh day a symptomatic patent ductus arteriosus was diagnosed and assisted ventilation increased. Despite restriction in fluid intake and treatment with indomethacin, the signs persisted and on the 18th day ligation of the ductus arteriosus was performed. Postoperative recovery was complicated by pulmonary collapse and consolidation. On day 21 he was weaned to continuous positive airway pressure of 5 cm H_2O.

Between day 21 and 31 extubation was attempted four times but on each occasion was unsuccessful. Stridor was followed by attacks of apnoea, episodes of bradycardia, and cyanosis and chest radiographs showed bilateral upper lobe consolidation. Bronchoscopy showed no vocal cord palsy or subglottic stenosis, but there was pronounced tracheal collapse on withdrawal of the bronchoscope, establishing a diagnosis of tracheomalacia. He remained stable while receiving continuous positive airway pressure for the next 10 days. At 6 weeks of age upper lobe collapse, fluctuating between the right and left lung, suggested bronchomalacia. On day 47 the endotracheal tube was removed twice, but reintubation became necessary after four and six hours, respectively.

Repeat bronchoscopy on day 58 again showed normal vocal cords without subglottic stenosis but pronounced collapse of the posterior wall of the trachea on expiration. Management continued with continuous positive airway pressure. From day 79 a regimen of alternating continuous positive airway pressure and spontaneous breathing through the endotracheal tube of humidified air/oxygen was begun. Initially, spontaneous breathing was allowed for five minutes each hour increasing to 20 minutes each hour. On day 86 after collapse of the right lung a third bronchoscopy was carried out. Secretions were removed and signs of tracheomalacia were still present. On day 108, at a postconceptional age of 42 weeks, he was extubated. This was followed by considerable inspiratory stridor and recession but no attacks of apnoea, and blood gases remained within the normal range. Stridor persisted, increasing when he was awake or agitated, but gradually diminished in intensity over the next month, and the fractional inspiratory oxygen was reduced from 0·35 to air. Upper lobe collapse and consolidation improved. Throughout the first 15 weeks he thrived on enteral milk feeds of his mother's expressed breast milk. Bottle feeding was successfully introduced on day 114.

He was discharged aged 5 months. He continued to have intermittent stridor but otherwise remained well and thrived. There were no abnormal neurological signs and cerebral ultrasound scans yielded normal results. At 18 months his stridor, though still present, is improving. He has had no appreciable infections and no hospital admissions and his development is normal.

Discussion

Tracheomalacia, which may be congenital or acquired, is defined as weakness of the tracheal wall from softening of the supporting cartilages with hypotonia of the myoelastic elements and may involve the whole of the trachea or occur as a localised phenomenon.[1] Only a few cases of acquired tracheomalacia have been reported in children less than 1 year of age and none in extremely low birthweight preterm infants. It may follow prolonged intubation, especially with a shouldered endotracheal tube, chest injury, external vascular compression, or tracheo-oesophageal fistula. In a series of 127 cases diagnosed by bronchoscopy 42 (32%) had major associated abnormalities and 55 (43%) had unilateral or bilateral bronchomalacia.[2] The commonest presenting signs were stridor or wheezy breathing, recurrent bronchitis, chronic cough, and cyanosis. Although acquired tracheomalacia cannot be excluded in the patient described, it seems unlikely as signs were of early onset and bronchomalacia was also present.

Congenital tracheomalacia exists in two distinct forms, a common mild variant and an uncommon severe form. The mild variant may be misdiagnosed as wheezy bronchitis or asthma in infants below 1 year of age. It represents an exaggeration of the normal softness and pliability of the tracheal supportive structures. A series of 15 cases showed that symptoms started from 5 days to 4 months and resolved with conservative management, without mortality, between 3 and 18 months.[3] A report of two term infants with severe bronchomalacia described successful management with 5 cm H_2O continuous positive airway pressure for 13 and 14 weeks, respectively.[4] A child with Larsen's syndrome has been reported in whom continuous positive airway pressure, given for 22 months, improved pulmonary mechanics.[5]

In four cases of severe tracheomalacia, diagnosed by broncoscopy, tracheostomy was performed between 1 week and 21 months of age.[6] Two had associated bronchomalacia and one died from an associated viral infection. A pronounced worsening of the symptoms with crying or agitation and upper respiratory tract infections was noted. The diagnosis of severe congenital tracheomalacia has been made by fluoroscopy or lateral inspiratory and expiratory radiographs. The latter may, however, be normal.[6] In the intensive care nursery bronchoscopy with a rigid ventilating bronchoscope will allow visualisation of the larynx, trachea, and major bronchi and enable aspiration of secretions. Intrinsic or intraluminal lesions can be excluded and the diagnosis made safely. Treatment with continuous positive airway pressure prevents bronchial collapse and in conjunction with physiotherapy may be required for an extended period until the bronchi become more rigid.

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Increased blood viscosity and tachypnoea in infants of diabetic mothers

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SUMMARY Tachypnoea was significantly more common in class B than in class A or C infants of diabetic mothers. Whole blood viscosity at a standardised packed cell volume and moderately low shear rate was significantly higher in infants of diabetic mothers with tachypnoea than in those without tachypnoea or healthy controls.

Infants of diabetic mothers often exhibit abnormal clinical findings in the early postnatal period, including hypoglycaemia and tremulousness, as well as tachypnoea, which may only commence several hours after birth. They also have a high incidence of polycythaemia, with an associated increase in blood viscosity.[1] Adults with diabetes may develop increased blood viscosity due to slightly raised plasma viscosity, decreased individual red cell deformability, and more pronounced red cell aggregation.[2 3]

We studied infants of diabetic mothers during their first two postnatal days to evaluate their blood viscosity independently of their packed cell volume, and to determine whether there was any relation between blood viscosity and tachypnoea in these infants.

Subjects and methods

Forty three infants of diabetic mothers with gestational ages between 37 and 41 weeks were selected at random after birth and followed prospectively. They were categorised according to White's classification of maternal disease.[4] Each infant was evaluated by random observations between 12 and 24 hours of age. Resting respiratory rates were counted for one minute intervals on at least two occasions during three to five minute periods of inactivity. The infant was classified as tachypnoeic if these rates were consistently ≥60/minute. A sample of venous blood, with dry heparin as the anticoagulant, was obtained within 36 hours of birth and studied on the same day. Blood from 27 term neonates served as controls. This was taken at delivery, or by venipuncture for clinical reasons, from infants who subsequently were found to have no major illness. Appropriate parental consent was obtained.

The packed cell volume of each blood sample was determined by a standard micromethod and was then adjusted to 50% (±1%) by addition or removal of an appropriate volume of autologous plasma. The standardised viscosity at specific shear rates was measured at 37°C in a 0·5 ml sample of blood by means of a Wells-Brookfield cone-plate viscometer (Model LVT) equipped with a 0·8° cone spindle CP–80 and was expressed in centipoise. During the latter part of the study, when the sample volume was sufficient, plasma viscosity was determined independently.

The incidence of tachypnoea in the categories of infants of diabetic mothers was compared by a χ^2 test with Yates's correction for small numbers, and viscosity differences at specific shear rates were evaluated by Student's *t* test.

Results

Fifteen of the 43 infants of diabetic mothers developed tachypnoea: three of 16 in class A, 10 of 17 in class B, one of seven in class C, and one of three in whom the class was uncertain. The incidence of tachypnoea in class B was significantly higher than in class A ($p<0·05$). There was no significant difference between the mean packed cell volumes of the infants of diabetic mothers with and without tachypnoea (58% *v* 57·2%). At the standardised packed cell volume of 50%, and at a moderately low shear rate ($11·25\ sec^{-1}$), the whole blood viscosity of those infants with tachypnoea was significantly higher than infants without tachypnoea and controls ($p<0·01$) (Table). At this shear rate—that is, $11·25\ sec^{-1}$—standardised whole blood viscosity in class B infants was higher than in controls ($p<0·01$). At the somewhat higher shear rate of $90\ sec^{-1}$, however, the above differences among the groups were not significant.

The limited number of studies performed on plasma showed a trend towards higher viscosity in infants of diabetic mothers with tachypnoea and in class B infants compared with controls, but the differences were not significant (Table).

Table *Standardised viscosity determinations in infants of diabetic mothers and control neonates. Values are mean (SD)*

	Controls	*Infants of diabetic mothers*					
		Grouped by class				*Grouped by respiratory rate*	
		All	*A*	*B*	*C*	*<60*	*≥60*
n=	27	43	16	17	7	28	15
Birth weight (kg)	3·27	3·55	3·65	3·39	3·49	3·54	3·57
	(0·44)	(0·63)	(0·61)	(0·68)	(0·53)	(0·69)	(0·71)
Venous packed cell volume (%)*	52·5	57·5	58·4	57·9	54·9	57·2	58·0
	(5·1)	(6·8)	(7·2)	(6·7)	(6·6)	(6·9)	(7·0)
Viscosity at 50% packed cell volume (cp)							
Shear rate (sec^{-1}):							
11·25	8·62	9·14	8·81	9·77	8·69	8·73	9·89
	(1·06)	(1·43)	(1·24)	(1·51)	(0·94)	(1·24)	(1·48)
90	5·14	5·27	5·20	5·39	5·19	5·17	5·45
	(0·39)	(0·58)	(0·59)	(0·54)	(0·50)	(0·51)	(0·68)
Plasma viscosity (cp)							
n=	14	12	5	7	–	5	7
Shear rate (sec^{-1}):							
90	1·28	1·37	1·29	1·42	–	1·30	1·41
	(0·19)	(0·15)	(0·14)	(0·15)		(0·13)	(0·16)
225	1·19	1·28	1·22	1·32	–	1·26	1·29
	(0·14)	(0·13)	(0·12)	(0·13)		(0·12)	(0·15)

*Postnatal sampling times not controlled; values not comparable for statistical purposes.

Birth weight: Controls (a) *v* all infants of diabetic mothers, $0·1>p>0·05$; (b) *v* class A infants, $p<0·05$.

Viscosity at 50% packed cell volume and shear rate 11·25 sec^{-1}: Controls *v* (a) class B infants; (b) infants with respiratory rate >60, $p<0·01$. Infants with respiratory rate <60 *v* infants with respiratory rate >60, $p<0·01$.

Plasma viscosity at shear rate 90 sec^{-1}: Controls *v* (a) class B infants; (b) infants with respiratory rate ≥ 60, $0·2>p>0·1$.

Plasma viscosity at shear rate 225 sec^{-1}: Controls *v* class B infants, $0·1>p>0·05$.

Discussion

The determinants of whole blood viscosity in vivo and in vitro are complex, involving both red cell and plasma factors. In the present study we observed an increase in whole blood viscosity in class B infants that was independent of their raised packed cell volumes, which was statistically higher than the controls at the moderately low shear rate (11·25 sec^{-1}) but not at the higher shear rate (Table). In general, our findings in infants of diabetic mothers were consistent with those described in adults with diabetes at similar shear rates.[2] The more pronounced increase in low shear viscosity possibly indicates mechanisms mediated by enhanced red cell aggregation, reduced erythrocyte deformability, or increased plasma viscosity. Decreased red cell deformability has been shown in blood from infants of diabetic mothers by Linderkamp *et al.*[5] The increase in plasma viscosity observed in our study did not reach significance, but this might have been related to the small number of samples.

The higher viscosity in class B infants compared with class A could be a reflection of either the severity and duration of the diabetic state in the mother, or, as seems more likely, of the efficacy of maternal diabetic control. Ongoing studies comparing viscosity with glycosylated haemoglobin concentrations should help to elucidate these differences.

The relation between viscosity and tachypnoea is of particular interest. Tachypnoea and respiratory distress have generally been regarded as clinical manifestations of neonatal polycythaemia (venous packed cell volume persisting above 65%) and as possible indications for a partial replacement transfusion in an infant with polycythaemia. A recent study on newborns with polycythaemia and hyperviscosity showed echocardiographic findings consistent with increased pulmonary vascular resistance that normalised after partial replacement transfusion.[6] It should be emphasised, however, that, although hyperviscosity with or without polycythaemia might represent a mechanism for the production of tachypnoea in infants of diabetic mothers, one cannot exclude the possibility that tachypnoea and hyperviscosity might each be independent neonatal variables reflecting the efficacy of metabolic control of maternal diabetes.

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The 'Sport-tester': a device for monitoring the free running test

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SUMMARY A cheap telemetric device, the 'Sport-tester', has been shown to be useful in monitoring the free running test for bronchoconstriction.

The free running test is one of the most potent bronchoconstrictive stimulants in subjects with bronchial hyperreactivity.[1] The test consists of running for six to eight minutes under standardised conditions, at a workload equivalent to 60–80% of the subject's maximal aerobic power.[2] Even though it is difficult to measure workload directly, an indirect estimate may be obtained by measuring heart rate during the exercise.[3] Hitherto, monitoring of heart rate during a free running test has involved the use of telemetry, which is generally expensive and therefore not widely employed. In the present study we examined a simple inexpensive form of heart rate telemetry during free running tests in children.

Subjects and methods

The device tested was the self monitoring 'Sport-tester PE 2000' (available in the United Kingdom from Duffield Medical Equipment Ltd, Belper, Derbyshire, at £97·90 + VAT), which consists of two parts (Fig. 1): (1) the 'transmitter', which is a battery operated electronic electrocardiogram (ECG) monitor strapped to the anterior chest wall with a rubber belt, and (2) the 'receiver', which is an electronic watch with an antenna housing, capable of receiving signals from the transmitter. The mean heart rate over five second epochs is displayed as a digital read out. Moreover, the receiver can store readings of heart rate every 30 seconds for up to 64 minutes for later recall. The subject must wear the receiver as a wrist watch while running, so that the receiver-transmitter distance is not more than one metre.

The reliability of the 'Sport-tester' was checked by comparing it with the readings of a standard ECG monitor (Kontron 105–000C) in 14 healthy children (eight boys and six girls) aged 8–12 years, who performed a submaximal treadmill exercise test while being monitored simultaneously by the 'Sport-tester' and ECG.

The 'Sport-tester' was then used to monitor the heart rate during two types of running: 'fast' running when the subjects were instructed to run as fast as they could and 'moderate' running in which they were asked to run at a comfortable pace. Twenty four normal healthy children (11 boys and 13 girls) aged 6–11 years participated. Each period of exercise lasted for six minutes, with an interval of 90 minutes between the two tests.

Finally, the 'Sport-tester' was used to monitor a group of 240 unselected children 6–12 years old, taking part in a fast free running test.

Results

The correlation between the results obtained from

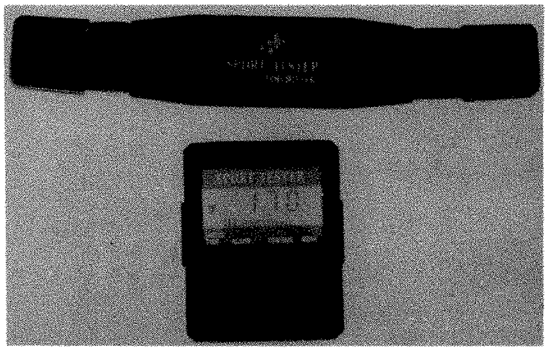

Fig. 1 *The 'Sport-tester', showing the transmitter (top) and the receiver (bottom).*

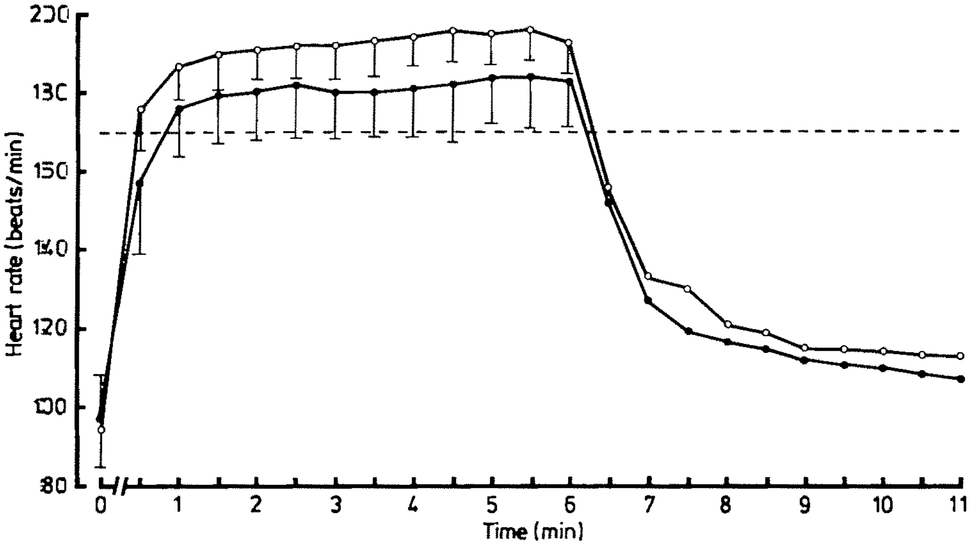

Fig. 2 *The heart rate recorded in 24 normal healthy children with the 'Sport-tester' during fast and moderate free running.* ○——○ *= Fast running,* ●——● *= moderate running. The dotted line represents a heart rate of 170 beats/minute.*

the 'Sport-tester' and the ECG was best described by a weak quadratic expression: $y=13{\cdot}3+0{\cdot}8x-0{\cdot}0008x^2$ ($n=167$, $r=0{\cdot}99$), where y is the 'Sport-tester' reading and x is the ECG monitor readings. Thus the 'Sport-tester' was a reliable indicator of heart rate even though it tended to overestimate at the extremes of the range and underestimate in the mid-range, but the deviation from linearity was not clinically important.

Comparison between fast free running and moderate free running showed that there was a similar pattern of heart rate response to both types of exercise, though the maximal heart rate plateau tended to be higher during the fast free running period (Fig. 2).

Monitoring the fast free running test in 240 children with the 'Sport-tester' was successful in 229 cases (95%). In every case the heart rate rose above 170 beats/minute within 30 seconds of the onset of running. In eight cases there was poor contact between the pulse transmitter and the skin, resulting in failure to record the heart rate. A further three children refused to participate after their skin had inadvertently been pinched while tightening the securing belt around the chest.

Discussion

Childhood asthma is still underdiagnosed and there is no simple objective method available to provoke bronchoconstriction in children.[4] Free running is a potentially useful test but involves an estimate of the workload while running. We decided to evaluate the 'Sport-tester' because of the association between heart rate and aerobic workload.[5] The results show that the 'Sport-tester' is a reliable and cost effective monitor of heart rate in this test. The device is readily tolerated by most children and when technical failure occurred it was complete.

Exercise induced bronchoconstriction is directly related to work intensity, and maximal post-exercise airway constriction follows a workload of 60–80% aerobic power.[6] This corresponds to a heart rate of more than 170 beats/minute, which was achieved in all the 229 children who successfully completed the free running test. Partial failure of the 'Sport-tester' would lead to an underestimate of maximum heart rate. There is little chance, therefore, of a false diagnosis of exercise provoked bronchoconstriction being made using this technique.

It could be argued that it would be desirable to use a monitor that was integral within the chest belt, thereby eliminating telemetry. This is not directly pertinent to the present study, which has shown the utility of a commercially available, fairly inexpensive device that is useful in the objective assessment of the free running test.

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High aluminium content of infant milk formulas

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SUMMARY The aluminium content of several commercially available infant milk formulas was measured by electrothermal atomic absorption spectrometry. Results were compared with those for fresh breast milk, cow's milk, and local tap water. Differences in aluminium concentration of greater than 150-fold were found, with the lowest concentrations in breast milk.

Because of its ubiquitous nature, aluminium has not traditionally been regarded as an essential trace element.[1] No cases of aluminium deficiency have been reported and minimum daily requirements for different ages are unknown. Fluids yielding as little as 7·5–15 µg of aluminium per day have been used recently without detriment, however, in infants receiving long term total parenteral nutrition.[2]

Aluminium toxicity in patients with chronic renal insufficiency undergoing haemodialysis or ingesting large quantities of phosphate binding gels is well recognised.[3] Recently, the high aluminium content of a proprietary milk formula was implicated as the cause of aluminium toxicity in two infants with neonatal uraemia.[4] In this paper we report the results of the measurement of aluminium in a variety of infant feeds.

Methods

Sample collection and preparation. Preprepared liquid and powdered formulas were sampled either directly from their glass containers or, in the case of preparations in cans, by collecting aliquots into acid washed polystyrene tubes. Each feed was sampled on two occasions and, where possible, from different batches. Breast milk was collected by lactating mothers directly into acid washed polystyrene tubes, using a no touch technique.

The powders were reconstituted in the laboratory by adding distilled, double deionised (aluminium free) water, using acid washed volumetric apparatus, to portions of accurately weighed milk powder.

Aluminium analysis. Aluminium was assayed by graphite furnace atomic absorption spectrometry employing a Varian Techtron AA975 and GTA 95 with autosampler.

All samples were initially diluted in the ratio of 1 volume of sample to 14·2 volumes of 0·3% analytical grade hydrochloric acid on an automatic diluter.

The aluminium content of samples was quantitated by the method of standard additions to allow for the variation in instrument response caused by the different sample matrices. Typically, a single random representative sample was used to generate a standard additions calibration curve for each analytical run. Subsequent samples in the run were quantitated by comparison with this curve. Samples yielding a mean peak height absorbance greater than the highest calibration point were further diluted with 0·3% hydrochloric acid until they fell within the calibration range.

The analytical technique was controlled with 'in house' aqueous and serum based control materials (method coefficient of variation at 80 µg/l was roughly 10%, run to run) and by participation in a national aluminium analysis quality control survey (Department of Applied Biology, Royal Melbourne Institute of Technology).

The spectrometer was operated in peak height

Table *Comparative aluminium content of infant feeds*

Sample	*Type of feed*†		*Aluminium content (µg/litre of feed)*‡	*Country of origin*
	Powder (µg/g)	*Liquid (µg/ml)*		
Breast milk		0·03	30	
5% glucose		0·04	35	
Tap water (four readings)		0·04	40	
Glucose-electrolyte mixture		0·04	40	
'Locasol'	0·23		85	Holland
Pasteurised cow's milk		0·09	95	Australia
'De-Lact Infant'*	0·50		105	Australia
'Lactogen'		0·17	105	Australia
'S26'*		0·14	125	United States
'Digestelact'*	1·01		165	Australia
'Similac'		0·20	200	Australia
'Alfare'	1·85		315	Switzerland
'Enfalac Premature'	2·17		335	Canada
'Nan'*		0·34	345	Australia
'Portagen'*	6·25		985	United States
'Infasoy'*	9·68		1335	Australia
'Glucose Nutramigen'*	11·49		1725	Australia
'Pregestimil'	11·80		1780	United States
'Isomil'		3·74	1890	United States
'Prosobee'		10·02	5080	Australia

*Samples taken from different batches.
†Aluminium content in µg/g (powder) or µg/ml (liquid) of feed. Mean of two measurements taken on separate occasions.
‡The calculated aluminium content per litre of feed diluted according to the manufacturers' recommendations (to 20 kcal/30 ml) with water assumed to contain 40 µg/litre of aluminium (using the measurements in column 1).

mode with no background correction required. Pyrolytic furnace tubes were used.

Contamination was controlled by ensuring that the peak height absorbance of a blank firing of 0·3% hydrochloric acid did not exceed 0·02 units relative to an air firing yielding a visually flat baseline.

Results

The results are shown in the Table. Fresh breast milk, 5% glucose, and a glucose-electrolyte mixture (both prepared in the formula room of our hospital) were found to have similarly low concentrations of aluminium comparable with known hospital tap water concentration.

Among the milk feeds, the mean concentration of aluminium ranged from 0·09 to 10·02 µg/ml for liquid feeds and 0·23 to 11·80 µg/g for powdered feeds. Compared with a litre of breast milk there was an increase of up to 165-fold in aluminium content per litre of reconstituted feed. Depending on the formula used, infants drinking a litre of milk daily would be exposed to between 30 and 5000 µg of aluminium per day.

Batch to batch variation and country of origin of the formulas did not seem to influence our results.

Discussion

Aluminium intoxication is now recognised as the cause of a progressive encephalopathy, vitamin D resistant osteomalacia, and one form of anaemia in the presence of chronic renal insufficiency.[3] Although these manifestations of toxicity were initially recognised in adults with uraemia undergoing haemodialysis, they were subsequently described in children who were receiving large doses of aluminium containing phosphate binding agents but who did not yet require dialysis.[5]

Less severe forms of neurological and intellectual dysfunction in infants developing chronic renal failure in the first year of life are well known. In fact, in one major study 20 of 23 such children were found to have developmental delay, microcephaly, hypotonia, dyskinesia, seizures, and electroencephalographic abnormalities on subsequent follow up.[6] Poor nutrition, raised serum parathyroid hormone concentration, subsceptibility of the infant brain to the uraemic environment, and aluminium toxicity were suggested as causes;[6] the possibility that the aluminium was derived from infant formulas was not considered.

More recently, cerebral aluminium accumulation has been documented in two infants with neonatal uraemia who developed a progressive and fatal encephalopathy in the absence of phosphate binding gels or dialysis with water appreciably contaminated with aluminium.[4] Both infants were fed with a proprietary milk formula that was found to contain high concentrations of aluminium relative to breast milk.

Our results confirm that infants may be exposed to appreciable amounts of aluminium from a variety of proprietary milk formulas, some of which contain more than 15 times the concentration of aluminium already implicated in cerebral toxicity.[4] This source of exogenous aluminium may contribute to other recognised forms of neurological and intellectual dysfunction in infants with chronic renal insufficiency. The effects of exposure to large quantities of ingested aluminium in infants with lesser degrees of renal impairment or normal renal function remain to be documented.

By comparison with phosphate binding gels, the total aluminium content of infant milk formulas is only modest. In the absence of other commonly recognised risk factors cerebral toxicity may therefore reflect a greater bioavailability of aluminium in milk formulas or an increased uptake of aluminium by the immature brain.

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Personal practice

General professional training in community child health

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SUMMARY A scheme providing general professional training for doctors in community child health is described. The scheme covers three years and gives broad clinical experience in general hospital paediatrics, community paediatrics, psychiatry, and general practice. The aims of the scheme and service needs and future structure for our trainees are discussed.

Over 4000 doctors work within the community child health services in Great Britain.[1] In spite of numerous reports and working parties,[2-8] health authorities have generally been slow to implement any training proposals for doctors in community child health comparable with those provided for other groups of doctors. Yet the clinical content is broad, including primary and specialist services,[9] statutory obligations with respect to education and social services,[10] and the complex task of liaison within and across professional boundaries. The Nottingham scheme is designed to provide a three year general professional training in community child health. The scheme operates within the recommendations of the Forfar report[8] and covers a three year period. The first trainee was appointed in February 1984.

Aims of the scheme

These are as follows:

(1) To provide a basic training in paediatrics.

(2) To show the need for knowledge about the local community to understand better the problems with which its inhabitants present.

(3) To provide knowledge about the service networks that exist both within and outside medicine in the community. This knowledge needs to be quite extensive, involving health, education, social services, and voluntary organisations. The outcome of service integration and interprofessional working can only be achieved through such knowledge.

(4) To provide a long term perspective. Although we are concerned about short term outcomes where acute problems arise, the concept of 'fit for the future' embodied in the Court report[4] should underlie the work of the community paediatrician.

(5) To emphasise the importance of health education and preventive medicine and to develop personal skills in this area.

(6) To encourage initiative and innovation in community child health practice.

(7) To develop insight into the difficulties of child rearing and to establish rapport and empathy with parents and children.

Outline of the scheme

The scheme contains the following personnel.

(1) Senior house officer in paediatrics at the University Hospital, Nottingham, appointed for six months, which is split into two month sections in paediatric accident and emergency, paediatric medicine, and paediatric surgery or orthopaedics.

(2) Senior house officer attachment in Inner City Community Paediatric Team, appointed for one year.

(3) Senior house officer in adult psychiatry, appointed for six months.

(4) Trainee in general practice (arranged through the Nottingham Vocational Training Scheme), appointed for one year.

The scheme uses existing training posts, other than the new one year attachment in community child health, which is funded from the child health budget. This takes place within the Community Paediatric Team, which provides services to part of the inner city area of Nottingham with a population aged 0–15 years of approximately 21 000. The whole team is linked to the University Department of Child Health. The team leader is a senior lecturer holding honorary consultant status. The organisation of the Community Paediatric Team is described elsewhere.[11] As well as the senior lecturer there are two lecturers, who have teaching and research commitments in the University in addition to their clinical responsibility in the community, two part time registrars (funded by the Regional Retraining Scheme), and the two senior house officer appointments.

The year in the community consists of three elements: supervised clinical experience in the community, attendance on the Nottingham University Day Release Course in Child Health, and a series of attachments to a wide range of other child or family centred resources. Table 1 shows the timetables of each of the two senior house officers, with rather more responsibility being given in the second six months.

The clinical experience consists of child health and school health services After a short introductory period of observation the work of the senior house officers is initially in parallel with the senior lecturer. The good clinic premises available enable two doctors to work in parallel so that the trainee has access to the senior lecturer for help with clinical problems. There is a weekly tutorial session at the end of one afternoon at which individual cases and general management issues are discussed. The trainees are encouraged to sit the Diploma in Child Health examination, and guidance on background study is given.

The Nottingham Postgraduate Course in Child Health has been running since 1976. It covers three terms of 10 weeks each. Term A covers the child and his illness, term B the child and his handicap, and term C the child and his behaviour. An average of 12 doctors from districts in the Trent region attend the course, coming from community child health, general practice, and hospital paediatrics. Information units and case histories augmented by slides are provided for each of the sessions and are read in advance. The course day consists of a discussion of the course units, which is usually led by a consultant, and often followed by practical demonstrations and visits—for example, to special schools. There is a multiple choice question paper at the end of each term and a research project is carried out by each course member over the year. These projects (a number of which have been published) are presented at an open meeting on the last day of each term. Each term is self contained so that the doctors can begin at the start of terms A, B, or C. In addition to the year course, there are also short skills modules on hearing/otorhinolaryngology, ophthalmology, and immunisation. Future skill related modules are planned in other areas—for example, developmental surveillance.

The attachments to other medical and nonmedical services are largely completed in the first six months. These are summarised in Table 2. They have served to provide knowledge about other disciplines and promote understanding and cooperation between agencies.

The attachment to the adult psychiatric service is to a consultant with both hospital and community responsibilities. It is our belief that psychiatry is an essential component of the training of every paediatrician. Problems presenting in children are often related to difficulties in their parents and do not arise de novo. A senior house officer post in child psychiatry is not available to our trainees as previous psychiatric experience is regarded as necessary for the appointment.

After the year as a trainee in general practice the doctor will have experience of children within the three medical settings in which they are seen: hospital, general practice, and community paediatrics. This should provide balanced knowledge and appreciation of the service as a whole.

Table 1 *Senior house officer—general timetable*

	Monday	*Tuesday*	*Wednesday*	*Thursday*	*Friday*
Morning:					
First six months	Primary schools observation/clinical practice	School clinic/ nursery classes	Postgraduate course and visits	Secondary schools	Visits
Second six months	Primary schools clinical practice	School clinic special school	Postgraduate course and project work	Secondary schools	Home visits
Afternoon:					
First six months	Clinical discussion/ primary schools	Child health clinic	Postgraduate course and visits	Child health clinic/ home visits	Visits
Second six months	Clinical discussion/ primary schools	Child health clinic	Postgraduate course and visits	Child health clinic/ home visits	Child health clinic

Table 2 *Summary of attachments to non-medical and medical services in the year's training, most of which are completed in the first six months*

Health
Dermatology
Ears, nose, and throat
Orthopaedics
Paediatric surgery
Ophthalmology
Chest clinic
Children's hearing assessment centre
Genetic counselling clinic
Child development centre
Growth clinic
Community nursing
Community health council
Child health unit administration
Health education department

Education
Classroom experience in primary and secondary schools
Special schools with community paediatrician:
  Moderate learning difficulties
  Severe learning difficulties
  Physical handicap
  Deaf
  Partially hearing unit
Education welfare service
Schools psychological service

Social work
National Society for the Prevention of Cruelty to Children special unit
Area social services team
Residential children's home
Observation and assessment centre

Discussion

Several outcomes are possible after completion of the scheme. Most doctors will be expected to work within community child health. The need for doctors in community child health will continue, though more specialist skills are likely to be required of them as general practitioners and community nurses take on some of the primary care functions. Some doctors will enter general practice, which has become increasingly interested in child health surveillance and prevention.[12] We acknowledge, however, that, although our candidates in theory have satisfied the requirements for postgraduate training in general practice, further experience in adult specialties would be necessary. Other doctors may wish to undertake further training in paediatrics, community medicine, or other specialties.

The scheme as outlined operates on a full time basis. We are also attempting to provide an equivalent training for other doctors on a part time basis. We see this as an area for further expansion for the training programme.

The programme puts great emphasis on training as well as the service content. We feel this is essential if high standards are to be attained in clinical practice. They are necessary if the development of community paediatrics is to continue. Many children are admitted to hospital for largely nonmedical reasons;[13] others are admitted for essentially preventable disorders or because of late diagnosis. We see community paediatrics as needing to address itself to these problems. Other developments might be a more community based service for handicapped children, paediatric home care services, and close working relations with general practitioners. Community paediatrics may also provide a more cost effective alternative to hospital outpatient care. (Tresidder J. Unpublished report.)

We recommend that each district should have training posts in community child health just as they do in other specialties. Appointments to career grade posts should be from those doctors who have completed this appointment or an equivalent training. The doctors in career grades (clinical medical officers, senior clinical medical officers, or consultant paediatricians in community child health) will provide the continuity of care of service while doctors in training posts will be appointed for fixed terms. One doctor in each district needs to carry responsibilities for training. Lastly, and essentially, adequate funds must be available to support initial training and further postgraduate medical education to maintain clinical standards.

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Special report

Screening for the detection of congenital dislocation of the hip

The last guidance on screening for the detection of congenital dislocation of the hip was published in 1969. Since then, results of various research studies have become available. The Standing Medical Advisory Committee and the Standing Nursing and Midwifery Advisory Committee agreed that the 1969 guidance needed to be reviewed and a Working Party was set up to recommend good practice in screening for this condition. This report has been accepted and endorsed by the full Committees.

This handbook is concerned only with screening for congenital dislocation of the hip and offers no advice on the clinical management of the condition.

Congenital dislocation of the hip encompasses varying degrees of instability, subluxation and dysplasia of the hip joint and should no longer be regarded in terms of simple "dislocation". The term is strictly speaking therefore inaccurate but is being retained because of its long standing usage.

Congenital dislocation of the hip (referred to in the following paragraphs as "CDH") is defined as

> "a congenital deformation of the hip joint in which the head of the femur is (or may be) partially or completely displaced from the acetabulum. The term embraces secondary hip dysplasia whether or not hip instability or dislocation persists"

A glossary of terms used is at Table 1.

It is estimated that in 15 to 20 per 1,000 live births there is evidence of hip instability at birth. However, in a large proportion of these cases the signs resolve without treatment in the first weeks of life. This does not guarantee normality however. Approximately 10% of unstable hips will persist to show classic signs of dislocation in infant life while a further 10% are likely to show evidence of dysplasia and/or subluxation.

It is clinically impossible to detect every CDH at birth. It is also impossible to identify those babies whose hips will not recover spontaneously. There must therefore be continuing surveillance *at least until the child is seen to be walking normally.* Guidance on how to undertake examinations for CDH at different ages is at Annex A. It is important that all health professionals who have responsibility for newborn babies and young children are:

1. aware of risk factors suggestive of CDH;
2. alert to the signs suggestive of CDH;
3. alert to observations made by parents;
4. able to ensure that all infants are screened in the way described in following paragraphs.

Accurate records should be kept whenever and wherever the examinations are carried out—at hospital, at home or elsewhere.

As outlined later in this handbook, a number of people from different disciplines are involved in screening for CDH. The statutory authorities and training bodies are invited to review training needs in the light of the recommendations contained in this handbook.

Aetiology and "at risk" groups

The hip joint develops during the first trimester of pregnancy and, in the absence of malformation, is initially a normal joint.

Table 1 *Glossary of terms and definitions*

Term	*Definition*
Congenital	Existing at or before birth
Dislocation	Displacement of articulating bones leading to a separation of joint surfaces
Hip	The articulation between the femur and the pelvis
Congenital dislocation of the hip	A spectrum of deformation of the hip joint, present at birth in which the head of the femur is, or may be, partly or completely displaced from the acetabulum. The term embraces secondary hip joint dysplasia whether or not hip instability or dislocation persists
Subluxation	A partial dislocation
Subluxable hip (Dislocatable hip)	A normally located hip which may be provoked into subluxation (or dislocation) by gentle manipulation (Synonyms—unstable hip, preluxation hip.)
Congenital malformation	A primary error in morphogenesis present at birth (an embryopathy)
Congenital deformation	An alteration, present at birth, of a previously normally formed part of the body (a fetopathy)
Dysplasia	An abnormality of development

In utero, the fetus lies in a flexed position. This physiological state changes only slowly during the first few months of life so that forced extension of the hips at, or soon after, birth may encourage an unstable hip to dislocate. It is reassuring to learn from the professions that normally babies are no longer held upside down by their legs after delivery. Such a practice is to be discouraged. Likewise, when measuring the length of a newborn baby, or if any surgical attention is required, care must be taken not to extend the hips forcibly. Tight swaddling of newborn babies should be discouraged as this holds the hips in extension and adduction and limits all movement. Newborn infants should whenever possible sleep in a prone position.

The condition is more common in girls and in first born babies. In addition the following factors place babies at greater than average risk of CDH:

(1) family history of the condition;
(2) infants presenting by the breech;
(3) other congenital postural deformities, such as those of the foot;
(4) births by caesarean section;
(5) oligohydramnios;
(6) fetal growth retardation;

and particular care should be taken to ensure that these babies are regularly examined at least until they are seen to be walking normally. However, in 40% of affected babies no risk factors are found.

When to screen

Screening for CDH should be regarded as an integral part of overall child health surveillance. As outlined in previous paragraphs, it is essential to re-assess the possibility of this condition until a child is seen to be walking normally. The child should always be undressed for these examinations.

The following times for screening are recommended and may coincide with other routine developmental tests.

Within 24 hours of birth. This examination is particularly important as some affected hips may temporarily lose the signs of instability shortly after birth. In view of the risks associated with excessive manipulation of the hip joint, duplication of the examination by both midwife and doctor should be avoided. Each maternity unit should determine its own policy in this respect to ensure that there is only one examination.

Arrangements should be made within each maternity unit to ensure that babies admitted to neonatal units, or babies who are to stay in hospital for only a few hours following delivery, do not miss this first examination. For babies born at home, the examination should be undertaken by the general practitioner (GP) or the midwife.

At the time of discharge from hospital. This will depend on the timing of the baby's return home but normally the second examination will be undertaken within 10 days of birth.

Written information on the examination for CDH should be sent together with information on any other tests undertaken in hospital, to the mother's GP and community midwife or health visitor as soon as possible following discharge. Full details should be recorded in the neonatal discharge record and parents should always be kept fully informed.

At 6 weeks of age. By this time the Child Health Record should have been opened. This examination and the examinations carried out at the times recommended in the following paragraphs should be carefully recorded in this by whoever undertakes them.

Between 6 and 9 months of age.

Between 15 and 21 months of age. Even if a child has been examined at earlier stages, this is a most important time as the child can be seen to be walking and some may now present with a limp or other abnormality of gait.

The child's gait should be reviewed at 2½ years and again at pre school entry medical examination.

Who should screen?

A number of health professionals may at some time have to examine a child's hips. It is important that whoever actually undertakes the examination should be proficient in the skill.

District Health Authorities should have a clear policy outlining who is responsible for undertaking the examination for CDH at the ages outlined above and for passing the results, or notification that the examination has not been done, to the GP and the community midwife or health visitor.

A designated officer within each District should keep the whole screening programme under review and record and evaluate the incidence of cases detected late. Such information should be made available to health professionals concerned.

It is important whenever an abnormality is suspected that the child is referred *without delay to a consultant with experience in this condition,* usually a paediatrician or an orthopaedic surgeon.

Training in the examination of a child's hips is of crucial importance. Although well-described in the literature, the techniques can be difficult to learn without experiencing the "feel" of the normal and unstable hip during the manoeuvre. The repeated examination of a neonate's hips for training purposes is not justified, particularly as this may cause damage in a hip that is already unstable. A training aid, in the form of a model of a newborn's pelvis, which simulates the "feel" of both the dislocated and dislocatable hip, is now available, although not on general sale within this country. (See Annex B for further details.)

Advice and support needed by parents

If an abnormality is suspected, parents will obviously be in some distress and may need advice from their GP and from other health professionals whether working in hospital or in the community. It is helpful if that advice is consistent and based on known fact.

Once the condition has been diagnosed parents will need to be advised of the natural history of the condition, the programme and probable length of treatment, follow up and the likely outcome. It may be helpful for health professionals to offer to put parents in touch with other families who have had a baby with the same condition. Above all, parents should be reassured that CDH is a treatable condition. It must also be never forgotten that the baby has the same needs in all repects as any other baby.

Health professionals should be aware of the need to counsel parents on the possibility of CDH occurring in future pregnancies. As mentioned in earlier paragraphs the incidence of CDH is many times higher than average if there is a family history of the condition. (Professor P S Harper's "Practical Genetic Counselling"—referred to in Annex B—gives specific figures on the risk of recurrence of CDH within a family.)

Future developments

The use of radiographic examination of the hips as part of a screening programme is contraindicated as it would result in an unacceptable number of infants being exposed to radiation. An ordinary AP radiograph of the pelvis will not usually demonstrate an unstable hip and therefore will generally be uninformative before a baby is 3 months old. *X*-ray examination of the hip is however most important for a child in whom a clinical diagnosis of hip displacement has been made.

Over the last few years much work has been done on the use of ultrasound scans in the diagnosis of CDH. Some centres in Europe now use the method in a neonatal screening programme and this work is now being evaluated in the United States and in the United Kingdom (see suggested further reading listed in Annex B). An ultrasound scan enables the examiner to evaluate and record the anatomy and some of the functions of the hip joint and such an examination can be undertaken soon after birth.

It is well recognised that instability of the hip evident at birth may disappear within 24 hours. An ultrasound examination may be able to act as an additional diagnostic tool at this stage since it has been demonstrated that a scan remains abnormal despite the absence of abnormal signs. It has also been shown that when a unilateral abnormality is present clinically, ultrasound may reveal deformation of both hips.

Annex A

Examination for congenital dislocation of the hip.

A. The signs of CDH, and hence the method of examination, vary with the age of the patient and the progress of the condition. In the early weeks of life usually the only abnormality present is hip instability, which may be detected by the Ortolani/Barlow manoeuvre. The classic signs of dislocation are not seen frequently in the neonatal period but become increasingly common thereafter. In the second year of life these signs include those of abnormal gait when the child has learnt to walk.

B. In examining for CDH it is essential that the infant or child be undressed from the waist downwards.

C. *The modified Ortolani/Barlow manoeuvre*

(1) This method of examination is of particular value in the neonatal period and up to the age of 3 months.

(2) The examiner's hands should be warm, the examination gentle, and the baby relaxed.

(3) The infant lies on his/her back with legs towards the examiner and the hips adducted and fully flexed.

(4) The hips may be tested for instability one at a time or simultaneously.

(5) Examination of each hip separately—see Figure 1 (page 924).

For examination of the left hip the examiner steadies the infant's pelvis between the thumb of his left hand on the symphysis pubis and the fingers under the sacrum.

The upper thigh of the left leg is grasped by the examiner's right hand with the middle digit over the greater trochanter, with the flexed leg held in

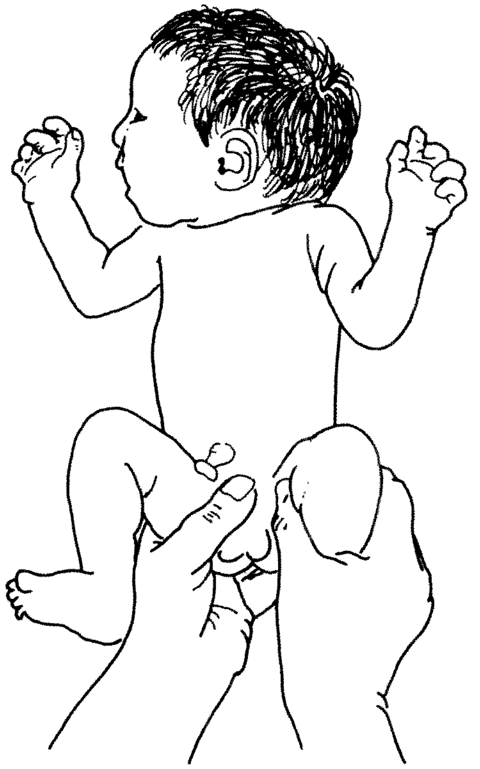

Figure 1

the palm, and with the thumb on the inner side of the thigh opposite the lesser trochanter.

An attempt is now made to move the femoral head in turn gently forwards into, and backwards out of, the acetabulum.

In the first part of the manoeuvre the middle digit is pressed upon the greater trochanter in an attempt to relocate a posteriorly displaced head of the femur forwards into the acetabulum. If the head is felt to move (usually not more than 0·5 cm) with or without a palpable and/or audible 'clunk', then dislocation is present.

The second part of the manoeuvre tests for subluxation (dislocatability). With the thumb on the inner side of the thigh, backward pressure is applied to the head of the femur. If the latter is felt to move backwards over the labrum (the fibro-cartilaginous rim of the acetabulum) onto the posterior aspect of the joint capsule (again a movement of not more than 0·5 cm and often accompanied by a 'clunk'), then the hip is said to be subluxatable (dislocatable).

To examine the right hip, the role of the examiner's hands is reversed.

(6) Examination of both hips simultaneously—see Figure 2 (below).

Instead of using one hand to steady the infant's pelvis, the examiner grasps both thighs as described above in section (5) and undertakes the Ortolani/Barlow manoeuvre on both hips simultaneously.

(7) Note that ligamentous clicks *without* movement of the head of the femur in or out of the acetabulum may be elicited in 5%–10% of hips and should be disregarded.

D. *Examination for classic signs of dislocation*

(1) The classic signs of dislocation may be present at birth. They become increasingly common after the first six weeks as the legs extend, the head of the femur displaces upwards and the soft tissues around the hip joint become shortened.

(2) The signs are much easier to detect when dislocation is unilateral as the abnormal leg may then be compared with the normal side.

(3) *Unilateral dislocation.*

Leg posture: the thigh on the affected side tends

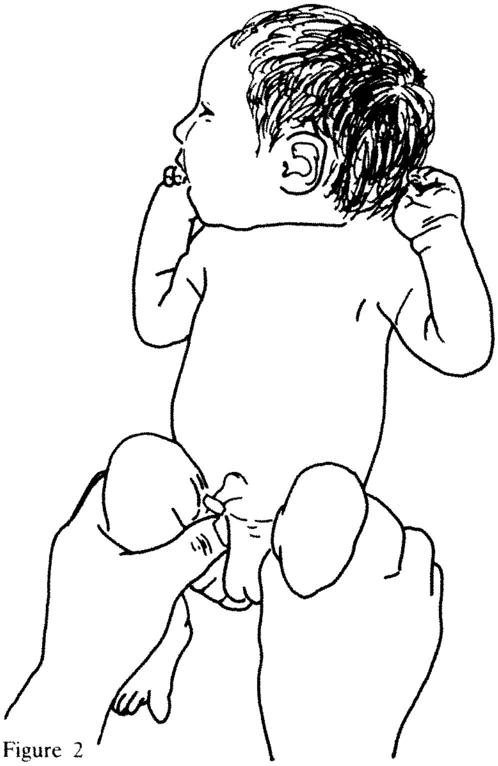

Figure 2

to be held in partial lateral rotation, flexion and abduction.

Limb shortening: there is above-knee shortening as compared with the normal leg. This is most apparent when the hips are flexed and the level of the knees compared (Figure 3, below).

Asymmetry of thighs: asymmetry of the junction of the thigh to the trunk as viewed from the front and of the skin creases on the inside of the thigh may be apparent.

Flattening of the buttock: when the infant is laid prone the buttock on the side of the dislocation may appear flattened.

Limitation of abduction: this is the most important sign of dislocation. The infant lies on his/her back with hips flexed at 90°. The thighs will normally abduct to about 75°. In the presence of dislocation abduction may be limited.

Hip instability: resistance to abduction may give-way with an Ortolani 'clunk' as the head of the femur reduces. Although hip instability gets progressively less common as the infant gets older, it may persist well into the second year. A push-pull manoeuvre of the femur may also be used to demonstrate the phenomenon of "telescoping".

(4) *Bilateral dislocation*. The signs are as above except that there is no normal hip for comparison. The upward and outward displacement of both thighs may leave a perineal "gap".

(5) *Gait*. Most children with CDH stand and walk at the normal time. However, approximately 20% of children with CDH will still not be walking at the age of 18 months (as compared with 5% for the whole population). Therefore, failure to walk by 18 months should prompt examination for CDH.

Unilateral dislocation gives rise to a limp. The child may fall to the affected side. When dislocation is bilateral the gait is waddling in character and there is a marked lumbar lordosis. Abnormality of gait is usually first noticed by the parents and their observations should be carefully checked.

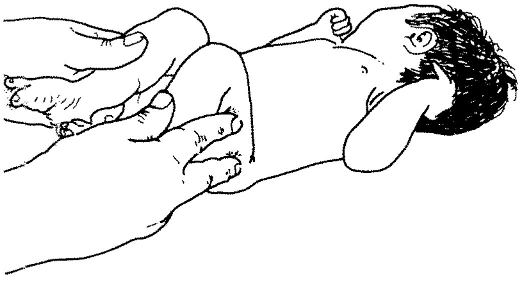

Figure 3

Table 2 *The relevant examination for CDH in relation to age*

Age	*Examination for CDH*		
	Ortolani/ Barlow	*Classic signs*	*Gait*
Within 24 hours of of birth	*	*	–
On discharge from hospital	*	*	–
6 weeks	*	*	–
6–9 months	–	*	–
15–21 months	–	*	*
24 months+	–	*	*

(6) *Trendelenburg sign*. The older child (2 years+) may be asked to balance on the affected leg. The hip abductor muscles, having no fulcrum to act on because of dislocation, cannot hold the pelvis level and it drops on the opposite side. The child, in an effort to maintain balance, leans towards the involved side. The Trendelenburg sign is then said to be positive.

Annex B

References and further reading

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Training Aid: "Baby Hippy". Enquiries to: Medical Plastics Laboratory Inc, Export Department, Med-

ica International, 205 West Wacker Drive (Suite 621), Chicago, Illinois 60606, USA.

Artwork produced by Peter Jack, Department of Teaching Media, Southampton University, from photographs provided by Dr P M Dunn, Bristol.

Prepared by the Standing Medical Advisory Committee and the Standing Nursing and Midwifery Advisory Committee Working Party (Professor C E Stroud (chairman), Dr S J Carne, Dr P M Dunn, Dr D W Fielding; Mr J A Fixsen, Dr E J Moore, Mrs M Morrell, Mr R E Robinson, Dr D J Stoker, Mrs J B Wilkes, Mr J A Wilkinson, and Dr D C McInnes) for the Secretaries of State for Social Services and Wales.

British Paediatric Association

Annual meetings

At York University:

1987 April 15–19
1988 April 12–16
1989 April 11–15

At University of Warwick:

1990 April 3–7
1991 April 16–20
1992 April 7–11
1993 April 19–23 (provisional)
1994 April 11–15 (provisional)

Archives of Disease in Childhood, 1986, **61**, 927–928

Correspondence

Medical care in severe mental handicap

Sir,

I wholeheartedly support Dr MacFaul's plea for continuation of National Health Service treatment facilities as a necessary back up to community care now that mental handicap hospitals are closing their doors.[1] Time and again one comes across situations requiring prolonged admission to the ward because of relapse in fit control, severe feeding difficulties, severe respiratory infection, deterioration in behaviour, and also emergency admission for short term respite care when social service provision fails, as it is more geared to planned placement. We try to cope with these problems in the acute paediatric ward, which is so busy dealing with acutely ill children that adequate observation and management of the handicapped child is considerably compromised.

While agreeing with Dr MacFaul that the paediatric department of a district general hospital has a role in the management of these children, it is necessary to point out that extra facilities will be required in the way of appropriate ward accommodation and nursing staff who have the appropriate skills. Such a unit (probably not more than 10 beds in size) would provide the flexibility of care (treatment and emergency short term respite care) that is so often needed, particularly for the profoundly handicapped. It is at times of crisis that parents most need help, and it is in these circumstances that the present pattern of care so often fails.

If the current philosophy of community care for the severely mentally handicapped child is to succeed then it is essential that a specific hospital resource is provided for them, and we as paediatricians should make the Department of Health and Social Security and local planners aware of this present lack of provision.

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Head circumference charts updated

Sir,

We have read with interest the report of Ounsted *et al* of a positive secular trend in head circumference from birth to 7 years.[1] We also have found that mean head circumference during the first year is about 1 cm greater than that presented in standard growth charts[2 3] and lies roughly on the 75th centile of the reference values.

One hundred and twenty six babies born in Cambridge in 1984–85 were measured at four weekly intervals throughout their first year, and measurements are continuing into the second year. Birth weights were all more than 2500 g and gestational ages over 37 weeks. Altogether, 65% were breast fed to at least four months, and solids were introduced at a mean age of 3·3 months. Disposable paper tapes were used, which in preliminary measurements compared with a steel tape gave readings of plus 1 mm, but the steel tape was considered unsuitable for use with young babies. Paper and fibreglass tapes, however, gave identical readings. The largest of two readings round the occipitofrontal circumference was taken.

The results, shown in the Table, are very similar to those of Ounsted *et al.*[1] Although 57% of the babies came from the non-manual social classes (I, II, and IIIN), there were no differences between these babies and those in the manual social classes (IIIM, IV, and V).

Table *Head circumference from 2 weeks to 1 year*

Age (weeks)	*No*	*Boys Mean (SD)*	*No*	*Girls Mean (SD)*
2	36	36·3 (1·3)	24	36·1 (0·9)
4	66	37·8 (1·3)	59	37·3 (1·0)
8	67	39·8 (1·2)	58	39·1 (1·0)
12	67	41·1 (1·1)	59	40·2 (1·0)
16	67	42·2 (1·1)	59	41·3 (1·1)
20	67	43·2 (1·2)	58	42·2 (1·2)
24	67	44·1 (1·1)	58	43·0 (1·2)
28	63	44·9 (1·2)	59	43·8 (1·2)
32	67	45·5 (1·2)	59	44·4 (1·2)
36	67	46·1 (1·1)	59	45·0 (1·3)
40	66	46·5 (1·1)	59	45·4 (1·3)
44	66	46·9 (1·2)	59	45·8 (1·3)
48	64	47·4 (1·1)	59	46·3 (1·3)
52	65	47·7 (1·2)	59	46·6 (1·3)

Growth charts for infancy in current use in the United Kingdom include the Gairdner-Pearson charts[2] as well as those of Tanner already discussed by Ounsted *et al.*[1] For the head circumference centiles from birth at 40 weeks to 2 years Gairdner and Pearson used the classical Harvard data, which was collected between 1929 and 1939. The more recently published centiles of the National Center for Health Statistics, adopted for international use, also include data originating from 1929.[3] We reiterate our plea that it is time that new charts were prepared for the present generation of babies to describe adequately the events that are taking place during this most rapid period of growth.

A A Paul,
E A Ahmed, *and*
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Dr Ounsted comments:

We entirely endorse the views of Dr Whitehead and his colleagues. Their head circumference findings are particularly important as they have shown elsewhere[4] that from 4 months onwards the weights and skinfold thicknesses of babies born in the 1980s and fed in a manner more or less in line with 'Present day practice in infant feeding'[5] were well *below* the median of the standards currently in use. Both studies draw attention to a positive secular trend in head growth in the last 30–40 years. Centile curves were created from our own data, and due to the relatively small numbers the 95% confidence limits were fairly large. Nevertheless, at no point from birth to 7 years did the 50th centile of the UK standard charts[6] fall within the confidence limits of our mean values for either sex. The differences between the two sets of data were greater for boys than for girls and more pronounced at the upper than the lower end of the distribution from 3 years onwards. Up to date charts are urgently needed for the assessment of head circumference growth in the present generation.

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[3] Hamill PVV. *NCHS growth curves for children, birth to 18 years.* United States Department of Health, Education and Welfare Publication PHS 78–1650, 1977.

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This correspondence is now closed—Ed.

Congenital hypothyroidism missed on screening

Sir,

The claim by Grant *et al* that three cases of congenital hypothyroidism were missed in the first five years of screening in Northern Ireland is a cause for concern.[1] Closer scrutiny of their data suggests, however, that all three cases should have been detected on the evidence available in the neonatal period. Thyroxine screening alone is generally recognised to be too insensitive. Nevertheless, whole blood thyroxine concentrations of 41, 38, and 53 nmol/l, respectively, are below the normal adult range, let alone the higher range documented for normal infants.[2] The fact that concomitant thyrotrophin concentrations were all <25 mU/l should not have deterred recall and further investigation even if congenital thyroxine binding globulin deficiency had explained the results. We would also question the wisdom of the whole blood thyrotrophin cut off value for recall. Our policy is to repeat a blood spot thyrotrophin evaluation from the same card for values between 10–20 mU/l; if confirmed in this range, a further blood spot is collected for analysis. Any value >20 mU/l dictates recall for a venous blood sample.

In the first five years of screening for congenital hypothyroidism in Wales 161 239 infants have been tested and 29 hypothyroid infants identified. The lowest blood spot thyrotrophin concentration in the hypothyroid group was 55 mU/l. To our knowledge, no cases have been missed. We wish to reassure paediatricians that the present screening policy used in most centres in Europe is reliable but never infallible. Clinicians should not hesitate to institute a further check on thyroid function if symptoms and signs of hypothyroidism are suspected.

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Turner's syndrome

Sir,

In Dr Brook's interesting article on personal practice in Turner's syndrome he states that there is often 'misapprehension about intelligence' in these patients and 'that an academic career is not precluded'.[1] He goes on to say that 'this is obviously in pronounced contrast with some of the other sex chromosome disabilities such as Klinefelter's syndrome'. This is another misapprehension. Since 1968 we have been conducting a longitudinal study of growth and development on children with sex chromosome abnormalities, including 19 boys with the sex chromosome constitution 47,XXY, ascertained by population screening and hence free of ascertainment bias. Three of these boys have verbal scores of 130+ on the Wechsler intelligence scale for children, as has one of four referred cases, so they may well proceed to academic careers. While it is true that the group as a whole shows a small but significant lowering of intelligence quotient compared with controls, there remains a relation between the child's cognitive ability and social class, as reflected in the occupation of the father.[2]

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rchives of Disease in Childhood, 1986, 61, 929–930

Book reviews

lf-injurious Behaviour: a collection of blished papers on prevalence, causes, d treatment in people who are mentally ndicapped or autistic. By G Murphy and Wilson. Pp 455: £9·95 paperback, £19·95 rdback. BIMH, 1985.

his book has three sections dealing with idemiology, aetiology, and treatment, ch with an introduction by the authors. hese introductions summarise the pre-ously published papers that follow and nount to an expanded review of the blished works. Of the list of references the authors' own papers in the collec-on, half also appear as papers in the ook.

The overall introduction defines self jurious behaviour as 'any behaviour, itiated by the individual, which directly sults in physical harm to that individual'. his is contrasted with stereotypes that use incidental injury. No mention is ade of parasuicide or self mutilation, ch as wrist cutting.

The subsections reflect the behavioural rientation of the authors. For example, ere are only two papers under the head-g 'Side effect of minor illness hypothesis', hile there are seventeen under the sub-eading 'Behavioural treatments'. Psychi-ric illness is not mentioned at all in the ctions on aetiology and treatment, and cial factors are not considered.

It is disappointing that the authors' troductions do little more than precis the apers. They do not adequately discuss e difficulties of epidemiology in relation heterogeneous groups of intermittent ehaviours. The discussion of 'diagnostic ategories' is rather narrow.

They explain that the papers were hosen for a variety of reasons and are not n exhaustive review. I was surprised that e AABT Task Force paper[1] was not only mitted but not even mentioned.

The authors' sections are easily read-ble, with a few printing errors. The list of eferences is useful, but the index is not ery detailed and is too similar to the list of ontents. Most of the papers are useful, nd the book as a whole is good value.

This book will be used as a review of the ublished reports and source of seminal apers by practitioners and trainees in ost disciplines who work with mentally andicapped people. It should be available in professional libraries in every district and in residential and day units dealing with mental handicap.

Reference

[1] AABT Task Force. The treatment of self injurious behavior. *Behavior Therapy* 1982; **13**:529–54.

N SIMPSON

Issues in the Care of Children with Chronic Illness. Edited by N Hobbs and J M Perrin. Pp 953: £72·25 hardback. Jossey-Bass Ltd, 1986.

This book of over 900 pages attempts to bring together all topics that relate to chronically ill children. Over 70 authors have contributed from disciplines that include paediatrics, education, sociology, nursing, psychology, and economics. The thread in common between these papers is the impact a chronically ill child makes on his family and on society. This book describes how North American society has responded over the last 20 years to provide a service to these children.

As the methods of health distribution and health funding and the educational systems have evolved differently in the United States British readers may find much that is not relevant to their practice. The cost of providing a service to children with handicaps of all sorts is discussed in detail and this comparative information may be of value to cost conscious paediatricians in all countries.

J J COGSWELL

The Lead Debate: The Environment, Toxicology and Child Health. Edited by R Lansdown and W Yule. Pp 286: £25·00 hardback; £14·95 paperback. Groom Helm, 1986.

The editors, both child psychologists, were members of the Lawther Committee, a Department of Health and Social Security Working Party that reported in 1980. This book is an attempt to explain and expand on that report and to include findings made in the intervening years. The basic chemistry, history, uses, distribution, measurement, and toxicology of lead are covered in a manner comprehensible to the non-medical or non-scientific reader but nevertheless with enough detail to satisfy anybody with an interest in the topic, whatever his or her level of expertise.

D P ADDY

Ear, Nose and Throat Disorders in Children. Edited by J E Bordley, P E Brookhouser, and G F Tucker Jr. Pp 446. Raven Press, 1985.

This volume is designed as a compact reference book that will be useful to paediatricians, general practitioners, resident trainees in otolaryngology, paediatrics, and family practice, and medical students.

As a general paediatrician I found it both too much and too little.

There is an introductory chapter on the mucous membrane and the hazards to which it is exposed. The various topographical sections (ear, nose and sinuses, mouth and pharynx, neck, and larynx) are introduced by, generally, well illustrated accounts of developmental anatomy and physiology.

Communication and its disorders are comprehensively reviewed and this comprises 30% of the total book. Insight is given into the mysteries of electrocochleography, electronystagmography, and tangible reinforcement operant conditioning audiometery, not to mention the laboratory assessment of vestibular function by a 'computerised sinusoidally rotating chair that relies on slow moving harmonic rotation.' Although some of this tends to leave the uninitiated slightly giddy, highly technical matters are well explained and the section also contains practical guidance on the child with communication disorder.

For the general reader, the scientific basis of ear, nose, and throat disorders is more than adequately covered.

What was disappointing, however, was the lack, in certain areas, of detailed guidelines on clinical management. For instance, there is nothing on the technique of laryngoscopy, although intubation of the trachea (in neonatal asphyxia) is the commonest vital ear, nose, and throat intervention a paediatrician has to undertake. Foreign body occluding the supraglottic larynx 'is usually fatal unless . . . treated successfully by first aid, as with the Heimlich manoeuvre'; but no account of this procedure is given. There are no details on the care of a patient with a tracheostomy. The paediatrician's nightmare of acute epiglottitis is not relieved by conflicting statements that 'identification of the condition can be made if the back of the tongue is well depressed', (page 377), whereas most would prefer the cautionary restraint 'the patient . . . may easily be completely obstructed by meddlesome use of a tongue blade' (page 415).

The orientation of the book is North American and those working in the tropics might be disappointed by the coverage of disorders such as diphtheria, tuberculous lymphadenitis, cancrum oris, Burkitt's lymphoma, or nasopharyngeal carcinoma.

Overall, this is a good book to have on the shelf of the hospital or departmental library. It is perhaps less useful to have at your elbow in a clinical dilemma.

D G D BARR

Pre-pregnancy Care—A Manual for Practice. Edited by G Chamberlain and J Lumley. Pp 279: £14·95 hardback. John Wiley and Sons, 1986.

There is more to pre-pregnancy care than the assessment of pre-existing maternal disease or genetic history. This book formulates the subject and considers in detail aspects such as smoking, alcohol consumption, exercise, and physical and mental stress in addition to the more routine anxieties of physical disease, previous obstetric performance, and genetics. The possible benefits of this field to both doctors and prospective parents are likely to be more important in future as the ideas crystallise more clearly.

NEIL MCINTOSH

Jacob's Ladder: A parent's view of Portage. By J M Lloyd. Pp 191: £9·95. D J Costello, 1986.

Janette Lloyd's son, Jacob, has Down's syndrome. The book describes the family's involvement with the Portage Project, a home based weekly intervention scheme for developmentally delayed children up to the age of 5 years. The complexities of observing and teaching Jacob are clearly and interestingly described, but in addition the family's other needs for services such as play groups are emphasised. This is an important book, giving a consumer's point of view of services.

HELEN MCCONACHIE

Orthotics—Principles and Practice. By G K Rose. Pp 237: £29·95. William Heinemann Medical Books, 1986.

The field of orthotics covers the manufacture and clinical use of splints, braces, and similar appliances. Few paediatricians have much knowledge or experience of this topic and are content to leave the prescription of orthoses to their colleagues in orthopaedics and physiotherapy, who in turn rely heavily on the expertise of the orthotist.

Gordon Rose was for many years consultant orthopaedic surgeon at the famous orthopaedic hospital in Oswestry and is chairman of the Orthotic Training Cou
He has made many original contribu
to the science of appliances and is prob
best known outside the world of o
paedics for his work on the hip guid
orthosis. His new book describes the
nical and clinical aspects of a wide va
of appliances. While some of these hav
relevance to paediatrics, others look
familiar (though before reading this b
would have had difficulty in naming
of them or describing their precise
tion). There are useful sections on
materials used and on the functional
tomy of joints, the foot, etc. The in
tions and complications of each treat
method are well described and are
trated with clear diagrams.

Orthotics—Principles and Practice is
marily intended for therapists, orthop
surgeons, and rheumatologists, al
whom will appreciate the wealth of ex
ence contained therein. The informati
perhaps too detailed for anyone ou
these specialties, and for the paediatr
it is rather heavy going. Certainly, al
the most conscientious of readers wi
tempted to skip the appendices on
biomechanics of the foot and on mate
science. Nevertheless, it would be a u
reference work in a child develop
centre and could be read with profi
anyone with a particular interest in
bral palsy, spina bifida, and other phy
handicaps. A few hours spent bro
through its pages would at least help o
disguise one's ignorance in a comb
orthopaedic-paediatric clinic!

DAVID

Monatsschrift
Kinderheilkunde
Organ der
Deutschen Gesellschaft
für Kinderheilkunde

134. Band
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Juni 1986

Springer-Verlag
Berlin Heidelberg New York Tokyo

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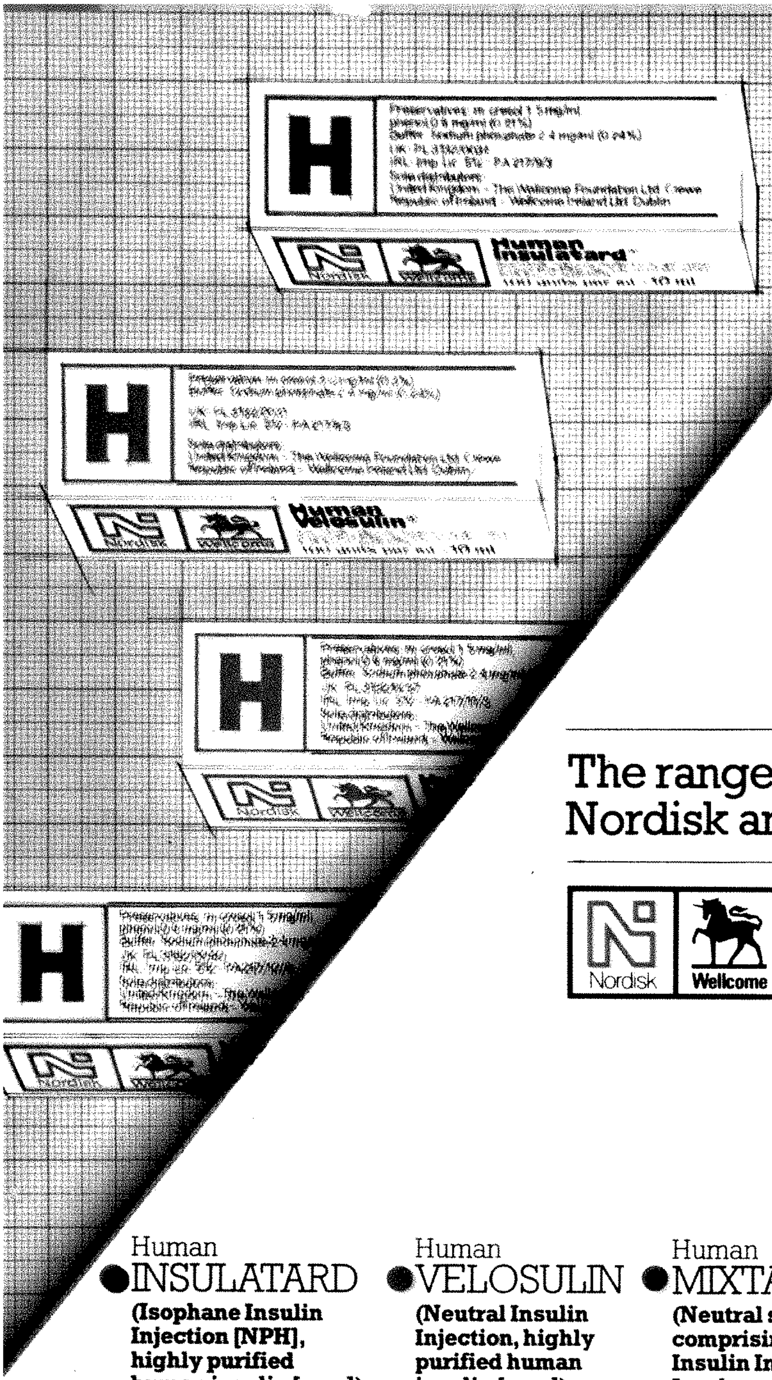

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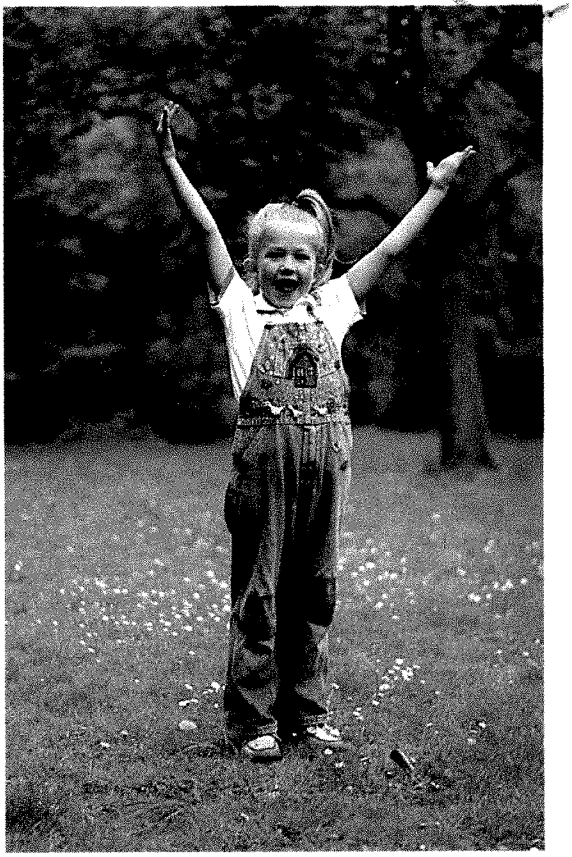

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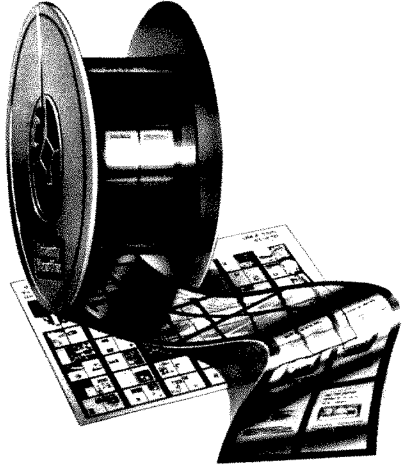

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creased or absent secretion of pituitary
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d by appropriate investigations of pituitary
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ituitary hormones may be exposed or exa-
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ituitary derived hormone, only in very rare
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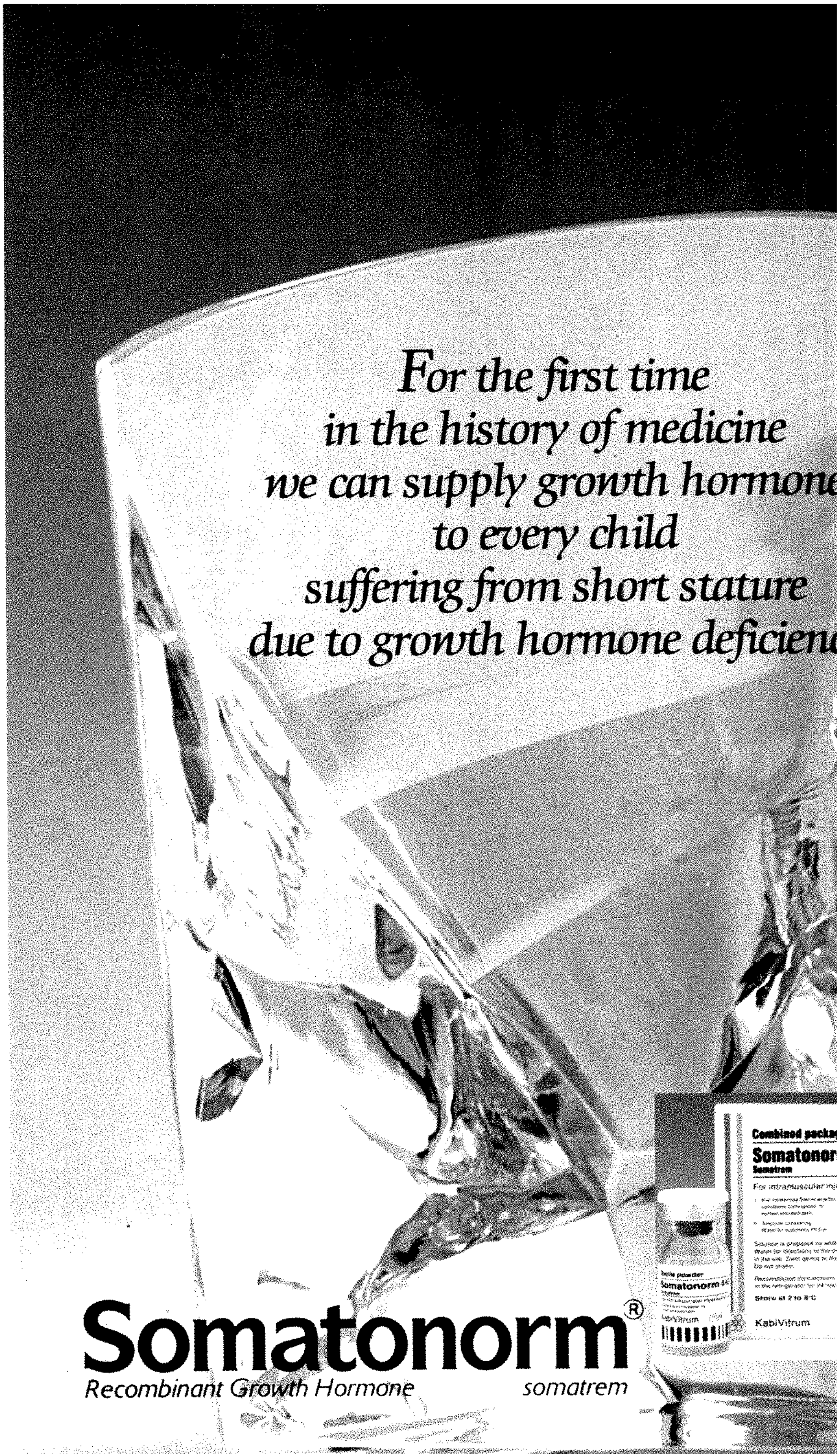
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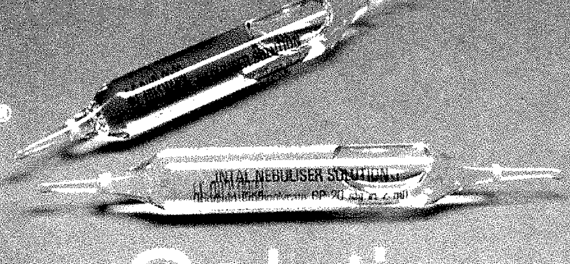

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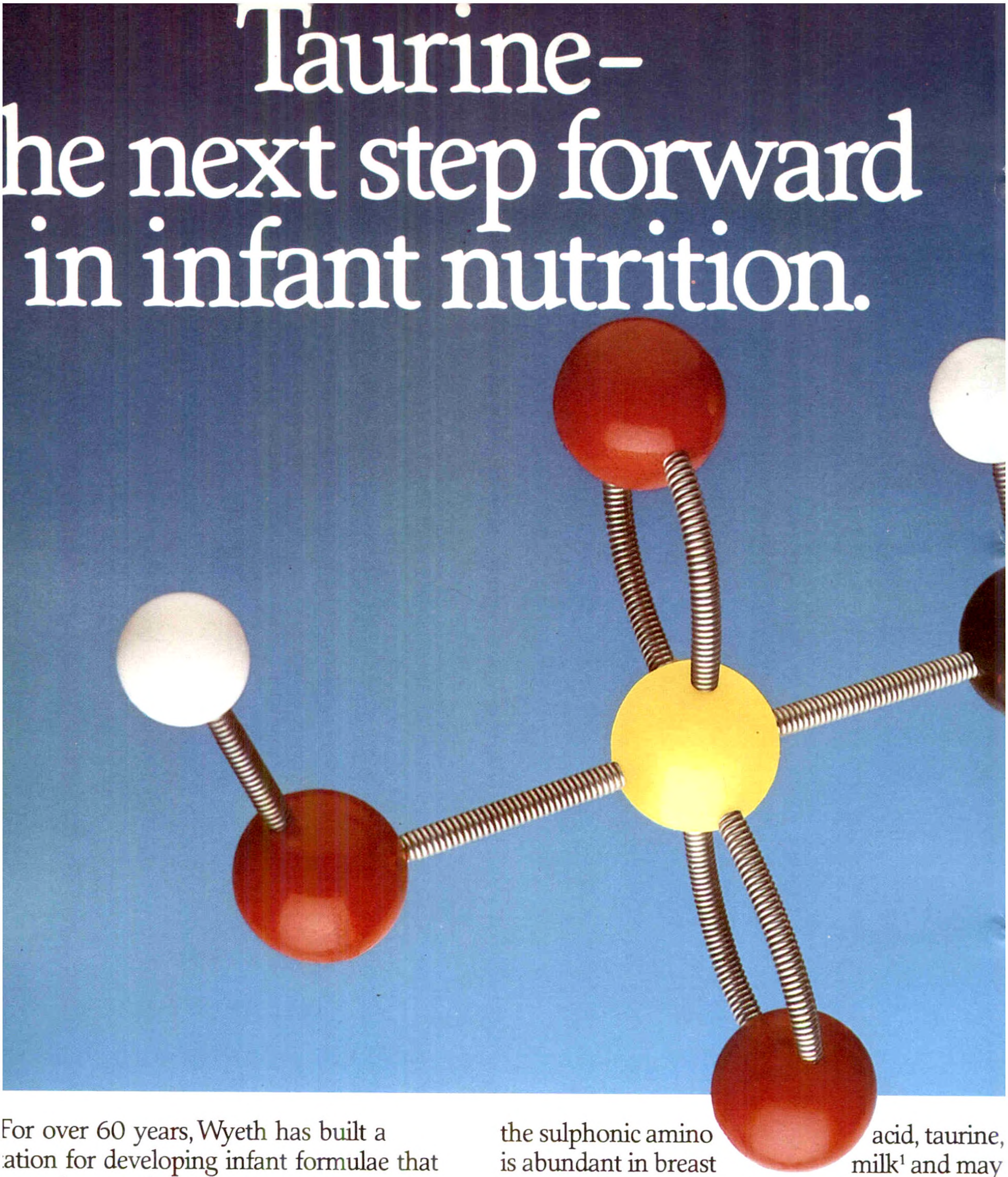

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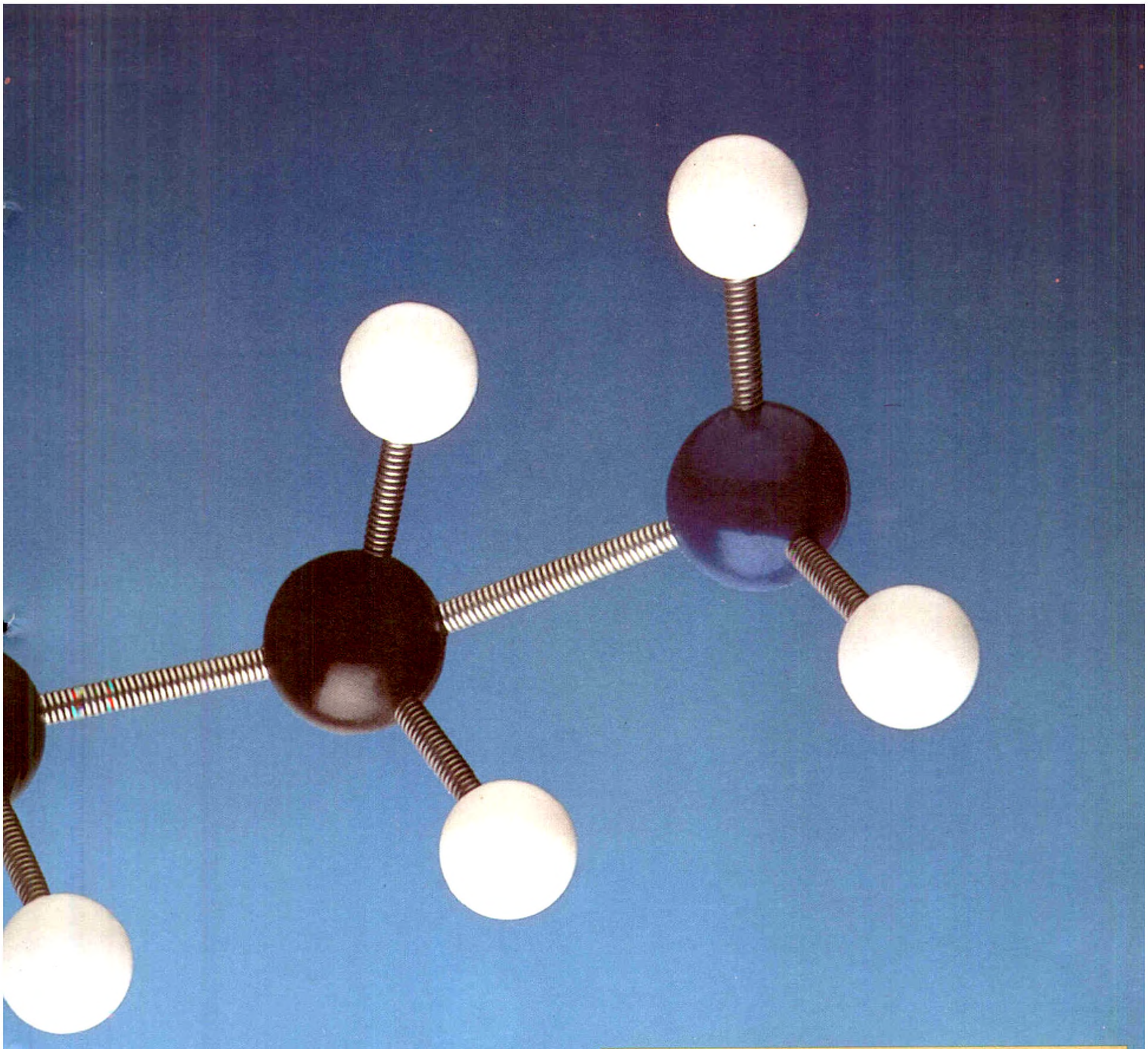

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References: 1. Rassin D.K., Sturman J.A., Gaull G.E. (1978). Taurine and other free amino acids in milk of man and other mammals. Early Human Development 2/1, 1. **2.** Jäavenpää A.L., Rasin D.K., Kaitunen P., Gaull G.E., Räihä N.C.R. (1983). Feeding the low birthweight infant: III Diet influences bile metabolism. Paediatrics 72, 677. **3.** Sturman J.A., Gaull G.E. (1976). Taurine in the brain and liver of the developing human and rhesus monkey. In: Huxtable R., Barbeau A. (eds). Taurine. Raven Press, New York, pp 73-84. **4.** Sturman J.A., Wen G.Y., Wisniewski H.M., Neuringer M.D. (1984). Retinal degeneration in primates raised on synthetic infant formula. Int. J. Dev. Neurosci. 2, 121. **5.** Huxtable R.J., Sebring L.A. (1983). Cardiovascular actions of taurine. In: Kuriyama K., Huxtable R.J., Iwata H. (eds). Sulfur Amino Acids: Biochemical and Clinical Aspects, Alan R. Liss, New York, pp 5-37.

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Presentation: Humulin S: A sterile, aqueous solution of human insulin (crb). **Humulin I:** A sterile suspension of isophane human insulin (crb). **Humulin Zn:** A sterile suspension of crystalline human insulin (crb) zinc suspension. **Humulin M1:** A sterile suspension of human insulin (crb) in the proportion of 10% soluble insulin and 90% isophane insulin. **Humulin M2:** A sterile suspension of human insulin (crb) in the proportion of 20% soluble insulin and 80% isophane insulin. Each presentation contains 100 IU/ml. **Uses:** For the treatment of insulin-dependent diabetes mellitus. **Dosage and Administration:** The dosage should be determined by the physician, according to the requirements of the patient. Humulin S may be administered by subcutaneous, intramuscular or intravenous injection. Humulin I, Humulin Zn, Humulin M1 and Humulin M2 should be administered by subcutaneous or intramuscular injection only. Humulin S may be administered in combination with Humulin I or Humulin Zn as required. **Humulin I, Zn, M1 and M2:** Rotate vial in palms of hands immediately before use to resuspend. **Mixing of insulins:** The shorter-acting insulin should be drawn into the syringe first, to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing. **Contra-indications, Warnings, etc. Contra-indications:** Hypoglycaemia. Under no circumstances should Humulin I, Humulin Zn, Humulin M1 or Humulin M2 be given intravenously. **Precautions: Usage in pregnancy:** Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. **Transferring from other insulins:** A small number of patients transferring from insulins of animal origin may require a reduced dosage and/or a change in the ratio of soluble to intermediate preparations, especially if they are very tightly controlled and bordering on hypoglycaemia. The risk of hypoglycaemia can be considered minimal if the daily dosage is less than 40 IU. Insulin-resistant patients receiving more than 100 IU daily should be referred to hospital for transfer. **Side-effects:** Lipodystrophy, insulin resistance and hypersensitivity have rarely been reported. **Legal Category:** P. **Package Quantities:** 10ml glass vials in packs of 5. **Price:** Humulin S: 100 IU/ml. £6.68; Humulin I: 100 IU/ml. £6.68; Humulin Zn: 100 IU/ml. £6.68; Humulin M1: 100 IU/ml. £6.68; Humulin M2: 100 IU/ml. £6.68. **Product Licence Numbers, Name and Address:**
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Date of Preparation: January 1986.

References: 1. Corcoran, J.S. and Yudkin, J.S. Diabetic Medicine, 1985, **2**, 131-133. 2. Fineberg, S.E. *et al*, Diabetologia, 1983, **25**, 465-469.

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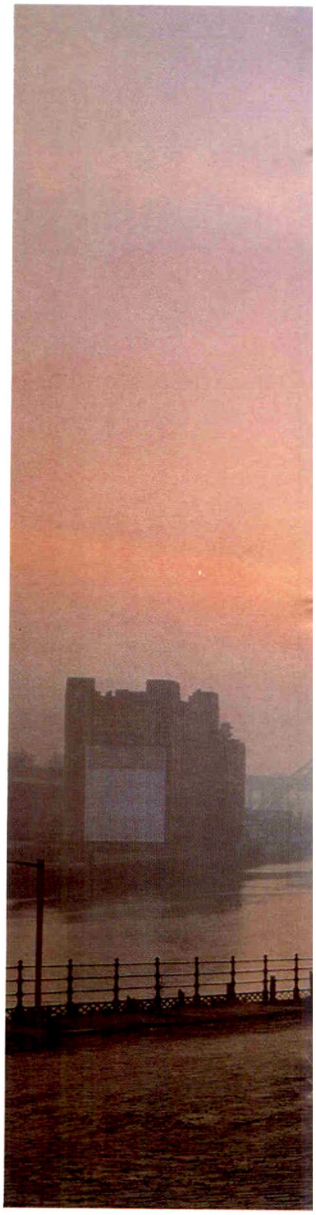

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3 day intervals until control is achieved.
aximum dose 2,500mg per day).
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h spaced increases until control is
hieved. (Usually within the range
30mg/kg body weight per day).
ldren under 20kg: 20mg/kg of body
ight per day; in severe cases may be
reased up to 40mg/kg day. Increases
ove this only if plasma valproic acid
els, clinical chemistry and haematological
ameters can be monitored. **Combined
erapy** It may be necessary to raise the dose
en used with anticonvulsants which induce
r enzyme activity. Dosage of barbiturates
uld be reduced if sedation is observed.
timum dosage is mainly determined by
zure control and routine measurement of
sma levels is unnecessary. **Contra-
ications, Warnings; Contra-indication:**
ive liver disease. **Side effects:** Liver
function including hepatic failure resulting
atalities has occurred in patients whose
atment included valproic acid or sodium
proate. The incidents mainly occurred during
first 6 months of therapy. Clinical symptoms are
re helpful than laboratory investigations
he early stages of hepatic failure. The
et of an acute illness, especially
hin the first 6 months, which may
ude symptoms of vomiting,
hargy or weakness, drowsiness,
rexia, jaundice or loss of seizure
trol is an indication for immediate
hdrawal of the drug. Evidence to
e does not establish which
estigation could predict this possible
erse effect: measurement of liver
ction should be performed in the
6 months of therapy in those who
m most at risk. Hyperammonaemia
hout hepatic damage can occur, it is
ally transient, but may occasionally
sent clinically. If so Epilim should be
continued. Valproic acid inhibits platelet
regation. Thrombocytopenia has been
orted. Spontaneous bruising or bleeding
n indication for withdrawal of medication.
creatitis, tremor, weight gain, transient
loss, increased alertness, aggressiveness,
eractivity, amenorrhoea, stupor and oedema
e been reported. **Drug Interactions** Epilim
potentiate monoamine oxidase inhibitors and
er anti-depressants. Loss of efficacy of oral
traceptive agents does not appear to be a
blem. **Women of Childbearing Age** Valproic
d and sodium valproate, like certain other anti-
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hese compounds should be weighed against the
sible hazard suggested by these findings and their
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Archives of Disease in Childhood, 1986, **61,** 931

Editorial

Sixty years young—a Diamond Jubilee

'The fields indeed are white unto harvest; the husbandmen are ready and skilful; the workers of bygone days hand on to them the sickle and wish them good luck and God speed. "He that soweth and he that reapeth shall rejoice together".'

With these stirring words Sir Thomas Barlow introduced the first edition of the *Archives of Disease in Childhood* in 1926. We are proud to celebrate the Diamond Jubilee and though there may be some pedantic paediatricians who will point out that we ought to be celebrating our 82nd birthday, rather than our 60th, since the *British Journal of Children's Diseases,* which amalgamated with us in 1944, began in 1904, nevertheless, we are content merely to celebrate our Diamond Jubilee today (for whoever has heard of having a special party for their 82nd birthday!).

Birthdays are times for looking back as well as forwards and in this issue we have invited some of our distinguished colleagues and members of the Editorial Committee to share our indulgence. In the mirror of the past we sometimes see the present more clearly.

We know that anniversaries are also a time for taking stock and that is what our Editorial Committee will do most seriously. Changes that will occur and that we hope will be beneficial for the Journal, however, should be gradual because the progress of our Journal has been steady and sure. We understand those who criticise the title, maintaining that *Archives* sounds old fashioned—dusty tombs in Vatican vaults—and that the rest of the title emphasises disease too much in these days when there should be more interest in disease prevention and in maintenance of child health. Nevertheless, the name of our Journal means something important to many people and when a speaker at a paediatric meeting refers to work that appeared in 'The *Archives*' everyone knows what that means and also the implied standard. The *Archives* has grown considerably from those early days 60 years ago: four times as many pages each year and a far greater international circulation. We are proud that the *Archives* has maintained its position within the top four for impact in the international Science Citation Index for paediatric articles (meaning that if an article is published in our Journal it has an extremely large chance of being read and quoted in a subsequent paediatric article in another international journal). Long may this be so, for it is a reflection of the high standards of those who do research and submit their work to us and of those who assess the papers.

Modern technology may seem a threat to scientific journals; but it is also an ally. Three years ago, and three years before Fleet Street, we changed from compositor set 'hot metal' type to computer setting. Last year we became the first specialist United Kingdom medical journal to be put on the American based Bibliographic Retrieval Services, which provides a data storage and computer retrieval service for journals. That itself was a recognition of our status as a core journal in the international medical literature, and it is that status that we believe will enable us to work with future advances in technology rather than be submerged by them. You cannot fight against the future, and 60 years gone, with even more to come, are on our side.

Anniversaries are a time for thanksgiving, and as Editors we thank our contributors, our hardworking referees whom we name on page 987, our loyal staff, and you our readers.

The cover pictures

Upper – Master Thomas R of Britain in 1926.

Lower – Miss K Piper of Europe in 1986.

(The photograph of Thomas R appeared on page 168 of the first volume in an article 'A case of Hypertelorism'.)

ARCHIVES OF DISEASE IN CHILDHOOD

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ARCHIVES OF DISEASE IN CHILDHOOD.

INTRODUCTION

BY

SIR THOMAS BARLOW, Bt., M.D., F.R.S.

The study of children's diseases differs from the study of other specialties of medicine, because its association with general medicine is more intimate and continuous than is the case in other specialties. This applies all along the line, to research, to clinical observation, to teaching and to practical therapeutics. A fair case indeed could be made for treating this subject as an integral part of general medicine, but for convenience of reference it deserves a notable place amongst special branches.

In an important address given some years ago by Dr. Gee on the history of the study of children's diseases, the claim was made that the great landmarks in the subject had been discovered and expounded by general physicians rather than by specialists. But during the last decade such important steps have been achieved in bacteriology, biochemistry and in clinical observation likewise, that the soundness of Gee's dictum, so far as the present generation is concerned, may now be disputed.

What reasons can be urged for the publication of "Archives of Disease in Childhood" in this country?

(1) Because of the necessity that the *conclusions* obtained by various workers and scattered through various publications should be rendered available; (2) because there ought to be an opportunity for keen workers in the many departments of children's diseases to publish and submit for criticism and verification their varied observations and experiments; and (3) because of the need to set forth in concrete and detailed form the results of new discoveries in diagnosis and treatment with a view to their employment in practice for the public good.

When we reflect on the generalisation which applies to the symptomatology of disease in child life and on the responsiveness of the child's nervous system we must deprecate any marked dichotomy of specialism in so far as the *organs* of the child are concerned. A more desirable classification in spheres of labour would seem to be based on the *different periods of child life.*

Pre-natal life; infancy reckoned from birth to the age of two years; early childhood, from two years to five years of age; late childhood, from five years to puberty, would seem to be a fair division.

Of these the pre-natal period in many ways seems the most important and far-reaching; obscure and limited as it is, some valuable additions have lately been made to our knowledge concerning it. The nutrition of the mother, considered exclusively as it affects that of the fœtus, may be very important indeed. It has been denied that there is any true fœtal rickets apart from osteogenesis imperfecta and achondroplasia. These two categories as well as early *fragilitas ossium* may be classified with developmental vagaries and associated with congenital malformations. But does true rickets sometimes begin in the *fœtal period*? It is noteworthy that in families in which several members are successively rickety the early children are least so, and the later children are increasingly so. This suggests that the mother's gradual failure in nutrition during successive pregnancies may play some part in the ætiology. The date at which the earliest tangible evidence of rickets becomes manifest may throw light on this question.

The trend of clinical observation and of therapeutic experience seems after all to point to the rickets with which we are concerned as mainly a post-natal and predominantly a food disease. The experiments on puppies performed by Dr. Mellanby would seem to place rickets amongst the "deficiency" diseases, the deficiency being in protein and absorbable fat and probably therewith the activating fat soluble vitamin A. The most efficient of all foods in the prevention of rickets in the infant period is admittedly mother's milk, but fresh cow's milk, cream, butter, suet, egg, dripping and animal fats have all to be reckoned with as useful and efficient substitutes under certain limitations. Animal fats are definitely superior to vegetable fats, butter being far better than vegetable margarine and cod liver oil than olive oil. The premature addition of carbohydrates to the infant's food would appear also to be a definite factor in this disease, and the dilution of cow's milk to which Dr. Still has drawn special attention, has probably been more responsible than we were at one time prepared to admit. Budin's contention with regard to infant feeding in favour of *undiluted cow's milk*—albeit in quite small quantities at a time and at more frequent intervals than the arbitrary "four hourly feeds"—demands careful reconsideration by English physicians.

Condensed milk, both sweetened and unsweetened, has been definitely condemned as an undoubted factor of rickets. Dried milk, on the other hand, appears to have secured a place as one of the fairly good substitutes in infant feeding, though further experience is desirable, especially in relation to infantile scurvy.

The cases of entirely breast fed infants who contract rickets would probably repay further investigation. Dr. Still attributes the rickety outcome in these cases to the extreme thinness of the mother's milk.

We now agree that Parrot's cranial bosses are truly rickety periostoses, though it is granted that the co-existence of the congenital syphilitic infection may render these and other rickety bone changes decidedly more pronounced. In the study of the pathology of rickets considerable attention has rightly been given to the changes in the epiphysial junction areas; but the rôle of the periosteum in the membrane-formed bones is equally important and, indeed, also the rôle of the periosteum of the shafts of the long bone. Hereditary syphilis is not the only co-operant form of lowered nutrition in the causation of rickets. Cretinism often shows marked combinations with rickety characters. Infantile scurvy is often grafted on rickets, and the occurrence of the complex of scurvy-rickets has been responsible for the delay in the accurate recognition of true scorbutic signs. Intercurrent acute specific illnesses, bronchitis and chronic gastro-enteritis, often cause aggravations and relapses of rickets.

Other important factors of this disease, namely, lack of sunlight and fresh air, and the sum total of what we describe as the results of overcrowding, have been long acknowledged, but the experience of Dr. Hess and his colleagues, and the post-war work of Miss Chick with the Vienna poor children, have given definiteness and emphasis to these factors. The remarkable therapeutic experiences of Dr. Hess and others, showing that the radiation of the mercury vapour quartz lamp can to some extent substitute direct sunlight in the cure of rickets, will probably have important results on practice. The recognition of the effect of ultra violet radiation in activating green vegetables and milk may likewise prove helpful.

With respect to infantile scurvy, in Great Britain the occurrence of this disease in a baby entirely breast fed is extremely rare, but there are records of foreign cases in which this occurrence seems to be undeniable. As in the prevention of rickets, it is very desirable that the pregnant mother should be able to secure for herself milk from cows fed on fresh grass and living largely in the open rather than stall fed, and that the food of the mother should also include a plentiful supply of fresh vegetables.

With respect to maternal syphilis, if there is the least reason to believe that there has been any former infection, a

Wassermann test ought certainly to be made, and if positive ought to be followed by definite treatment. The results of inoculation of the mother, with one of the arseno-benzol preparations given regularly from the earliest period of pregnancy up to the time of delivery, have proved strikingly beneficial by way of immunisation to the infant.

When artificial feeding has to be adopted either wholly or in part, the question of boiling cow's milk requires decision. Repeated boiling, like repeated sterilisation, is certainly wrong. When infantile scurvy has become manifest in a given case any boiling whatever probably reduces the anti-scorbutic efficiency of milk, and unboiled milk in small quantities can be tolerated often with remarkable success. But a single boiling, just before the feed is given, is generally safe and wise. With regard to the anti-scorbutic additions, potato roasted in the skin and the mealy part of the potato scraped and sieved into milk, has proved satisfactory as the initial measure. Orange juice or grape juice are useful adjuncts, and good meat gravy, or home-made meat juice, are likewise of service as additions to the milk. Boiled yolk of egg is a useful standby. With regard to proprietary foods and their relation to infantile scurvy, there is little new to be said, except that they retain their supremacy as amongst the chief offenders in the causation of the disease.

Amongst the practical problems of the period of infancy (that is from birth to two years of age) artificial infant feeding is surely the most insistent and most difficult to carry through on anything like sound lines. None of the alimentary problems has commanded more zeal and patient investigation than what we have provisionally agreed to describe as congenital hypertrophy of the pylorus or otherwise as hypertrophic stenosis of the pylorus. Dr. Cameron has indeed pointed out in his admirable Lumleian lectures that neither of these names is satisfactory or indeed strictly correct. Further knowledge is needed in order to define in any accurate descriptive title the true notes of the disease.

No doubt Hurst's original work some years ago, on the mechanism of the alimentary canal and his contention for what he has called Achalasia (which has been defined as the absence of relaxation) gave a direction to enquiry, although he was not specifically concerned with this disease.

The two doctrines held as to the pathology of hypertrophic stenosis of the pylorus may be defined as (1) that of Hirschsprung supported by Cautley, according to which there is a primary hypertrophy of the pylorus; (2) that of John Thomson, according to which there is inco-ordination of the muscles concerned in contraction and consequent propulsion of the food content and the relaxation beyond, which permits of the initial propulsion becoming operative; in other words, there is disharmony and inco-ordination between the stomach wall and the pylorus. With regard to Hirschsprung's and Cautley's contention it may be said that hypertrophy independently of antecedent obstruction or resistance is not in harmony with what we know of pathology in other regions. With regard to Thomson's ingenious hypothesis (which it may be mentioned he has also applied to the explanation of hypertrophic dilatation of the colon), it may be observed that it carries the difficulty back to the enquiry what then is the cause of this disharmony and inco-ordination and how is it brought about? But although the pathology of this disease is still doubtful we owe a great debt to the British school for the elucidation of its natural history and for the important fact that we no longer regard it as a hopeless and insoluble mystery, but as a morbid entity which is capable in very many instances of complete restoration. Dr. Nicoll, of Glasgow, had the great merit of introducing in his case in 1900 Loreta's operation of dilatation of the pylorus which was successful; according to Dr. Thomson this patient made such a good recovery that eighteen years afterwards he was passed as a sound life for the Army.

Thomson, Still, Cameron and Cautley, with the invaluable help of their surgical colleagues, Stiles, Burghard and Dent, have added a real chapter to medicine, nor can we forget the important contributions of Holt, Hirschsprung, Dufour and Fredet, and on the surgical side the brilliant contributions of Rammstedt.

It is most important, and indeed invaluable, that the indefatigable workers at this disease have established the two clinical features which are imperative in the diagnosis, namely, (1) the demonstration of a visible stomach peristalsis, and (2) the palpation of a definite resisting tumour due to the pylorus which is in a state of spasm. Grasping these fundamental conditions, what are the chief indications for medical treatment of an early and moderate case of this disease? (1) The maintenance of breast feeding, maternal if possible, or that of the wet-nurse; (2) small feeds and, if necessary, at shorter intervals than normal; (3) the employment of stomach lavage once or twice daily, but guided as to frequency by the varying incidence of stomach dilatation and food delay. In a fair number of cases these methods have proved successful. The real trouble being caused by what is equivalent to a mechanical difficulty, alteration in the composition of the feed is not indicated, and it is noteworthy that in the typical favourable case signs of food toxæmia in the early stage are conspicuously absent. If under these methods there is no amelioration, and the vomiting increases in severity with rapid wasting and threatening of toxæmia, then surgical aid should be invoked. Also, if from the onset the case is acute, primary surgical operation would appear on the whole to give the best chance.

Some of the surgical procedures which were employed in the early cases, for example gastroenterostomy, have now been negatived, and there remain two from which excellent results have been obtained, (1) Laparotomy, followed by Loreta's method of dilatation of the pylorus (Burghard and Stiles); (2) Laparotomy followed by longitudinal incision of the peritoneum over the pylorus and of the muscular fibres down to but *not through* the mucous membrane, so that no opening is made into the stomach (Rammstedt).

Rammstedt's operation seems at present to command most confidence, but this is a matter in which the personal equation and experience of the operator must count for a great deal.

There is not adequate space in this introduction to refer to many other important additions which have been made during the last decade to the pædiatric outlook, both medical and surgical. The juvenile type of acute and sub-acute rheumatism requires a chapter of its own, and supplies in fact a fuller and certainly more interesting survey than the ordinary rheumatic fever attack of the adult. This is one of the cases in which the study of children's diseases contributes illumination to general medicine. The work of Poynton and Payne challenges candid re-consideration. What valid objections can be raised to their technique and to the soundness of their general contentions? The treatment of the convalescent period of acute and sub-acute rheumatism in the child and the precautions to be taken regarding the insidious incidence and increase of endocarditis merit patient enquiry and therapeutic experiment.

Great progress has been made in the orthopædic surgery of the deformities left by poliomyelitis. The subject of immunisation which began long ago with diphtheria, has made bold strides and has a great future. The recent work associated with the names of Schiff and Dick will at once occur to the modern reader.

The fields indeed are white unto harvest; the husbandmen are ready and skilful; the workers of bygone days hand on to them the sickle and wish them good luck and God speed. "He that soweth and he that reapeth shall rejoice together."

Archives of Disease in Childhood, 1986, **61**, 939–940

A STUDY OF RICKETS; Incidence in London.

BY

DONALD PATERSON, M.B. (Edin.), M.R.C.P. (London),

AND

RUTH DARBY, M.B., Ch.B. (Birm.).

(From the Infants' Hospital, Westminster.)

In order to ascertain the incidence of rickets in London a study was attempted during the months of February, March and April of 1925.

It was thought that these being the darkest months of the year, following on a long, sunless period, the incidence of rickets would be at its height.

Our first difficulty was to define the basis upon which rickets could be diagnosed. We had over and over again diagnosed rickets clinically . . . .

Commentary

J O FORFAR

The *Archives of Disease in Childhood*, although it became the official journal of the British Paediatric Association (BPA), was first published two years before the founding of the BPA. Appropriately, the senior author of this paper on rickets, Dr Donald Paterson, played a leading part in the founding of the BPA and was its first Secretary. He was a Canadian who came to Edinburgh University to study medicine. After qualifying there he moved to London where he worked for many years at Great Ormond Street and the Westminster Hospital, becoming a leading figure in British paediatrics. Dr Hector Cameron in his history of the British Paediatric Association 1928–1952 says of Donald Paterson, 'Under the smoke-screen of his magnificent hyperbole and invective, he judged shrewdly of every situation. He had determined to found a Paediatric Association for all Britain and nothing was in the least likely to stop him.'

The paper examined the incidence of rickets in children attending hospitals over the months of February, March, and April, months in which the incidence of rickets was known to be highest. Children up to the age of 2 years attending the Infants' Hospital, Westminster, and St Thomas's Hospital were examined clinically and had an *x* ray of the wrist taken. Of the 339 children attending, four (1·2%) showed active rickets clinically and radiologically and 110 (32%) showed evidence of previous rickets clinically, although radiologically the rickets was shown to have healed. No evidence of rickets either clinically or radiologically was found in 225 (67%). Interestingly from a social point of view, another paper in the same issue of the *Archives* (by Drs W P T Atkinson, Helen Mackay, W L Kinnear, and H L Shaw) showed that children of the same age from a poorer part of London, attending hospital, showed an incidence of active rickets of 8%.

Although the title of Dr Paterson's paper emphasises a concern with incidence, an equally important element with which it deals is the preventive and curative effect of cod liver oil. Of the 339 cases studied, 313 (92%) had had some cod liver oil over a considerable period, indicating the extent to which at that time a prophylactic or therapeutic measure of this kind had been widely adopted by the public. Those of us whose early childhood spans that era remember with some revulsion the twin oils that were then so prominent in the family medicine chest—cod liver oil, so widely employed as a universal promoter of childhood health, and castor oil, so ritually administered as a cure for any childhood ill. None of the four active cases described in Dr Paterson's paper had had cod liver oil. Of the healed cases, 88% had had cod liver oil, leading to the assumption that this oil had cured their rickets, but no evidence is provided that there was a temporal association between the administration of the cod liver oil and the cure of the rickets. The assumption might have been strengthened had the authors subjected their data to the discipline of the statistical analysis that would now have been imposed on them. This would have shown that there was a significant difference ($p<0\cdot05$) between the 96% incidence of cod liver oil consumption in the cases without any evidence of past or present rickets and the 88% incidence in healed cases. There was clearly a difference between the two groups, but the reason for it cannot be determined with any certainty from the data given. It is doubtful if the conclusions drawn, correct although they may have been, would have satisfied the standards of logic demanded by present day editors of medical journals—even the gentle, friendly paediatricians who today control the editorial destiny of the *Archives* are seen by some to metamorphose at times into ruthless martinets as they set about culling sophistry from its pages.

Medicine contains many examples of the discovery of cures before any understanding of their scientific basis was possible. Cod liver oil for the treatment of rickets was a classic example, as were fox glove extract for the treatment of the 'dropsy' of cardiac failure, raw liver for the treatment of pernicious anaemia, and lime juice for the treatment of scurvy. Vitamin D is not mentioned in the article as that word was not yet in common currency and the chemical nature of vitamin D had yet to be discovered. This had to await the discovery of the specific sterol irradiated ergosterol or calciferol five years later and the demonstration that it could prevent and cure rickets. At that time and for many years thereafter that discovery seemed the final word on the subject of vitamin D. Much, however, remained to be discovered and has been discovered over the past few years. The individual response to vitamin D has been found to vary widely — the same intake of vitamin D may be adequate for one child and result in rickets in another; a vitamin D intake associated with health in one child can result in hypercalcaemia in another. Vitamin D dependent rickets and idiopathic hypercalcaemia of infancy represent extreme ends of this spectrum. The explosion of knowledge regarding the metabolism of vitamin D over the past few years has revealed that naturally occurring vitamin D—7 dehydrocholesterol converted in the skin by sunlight to cholecalciferol (vitamin D_3)—is only active if hydrolysed in the liver to 25-hydroxycholecalciferol (25-hydroxyvitamin D) and then further hydroxylated in the kidney to 1α, 25-dihydroxycholecalciferol, the active form of the vitamin.

From a diagnostic and a therapeutic standpoint the discovery of these metabolites of vitamin D has been important. Before their recognition the estimation of vitamin D could only be made on the basis of a biological assay, inaccurate, difficult to standardise, and expensive. The ability to measure these metabolic products of vitamin D accurately, particularly 25-hydroxycholecalciferol, has been an important factor in recognising and categorising different types of rickets. From a therapeutic point of view the availability of analogues of 25-hydroxycholecalciferol where hepatic disease is a cause of rickets and of 1α, 25-dihydroxycholecalciferol where renal disease is the cause has added greatly to the armamentarium available for the management of different types of rickets.

Man is indebted to the cod for more than one of the cheapest types of protein. Cod liver oil enabled him to prevent and cure a disease that for centuries ravaged the health of children. Although rickets was first described nearly 250 years ago, the piscatorial saga that led to its prevention and cure has only been told over the past 60 years. To that saga the *Archives of Disease in Childhood* has contributed many important chapters.

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Archives of Disease in Childhood, 1986, **61,** 941–942

HEPATIC CIRRHOSIS IN CHILDREN,
with special reference to the Biliary Forms.

BY

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AND

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The occurrence in hospital within a comparatively short space of time of four unusual examples of cirrhosis of the liver in young children has led us to make this communication.

Disorders of the liver in childhood have in recent years not attracted much attention in this country, and we feel that the mere ventilation of the subject, though we may have little new to add, may serve a useful purpose.

It is possible that others besides ourselves have been inclined to be guided in their views upon cirrhosis of the liver by a recollection of cases of alcoholic cirrhosis in the adult, and to recall such symptoms as . . . .

Commentary

A P MOWAT

The paper starts modestly with four case reports of children with chronic liver disorders recently intensively investigated by the authors but without reaching a diagnosis. Stimulated by this failure and by their concern that disorders of the liver in childhood had not attracted enough attention in this country, the authors have produced a very readable review of the subject as perceived in 1926.

Succinct case histories enhanced by superb photomicrographs illustrate descriptions of seven forms of cirrhosis. Much of the review remains as apposite as when written. Among the non-biliary forms they included multilobular cirrhosis, Banti's anaemia, Wilson's disease, and, somewhat surprisingly, icterus gravis neonatorum. They recognised that the latter was not associated with cirrhosis but thought it should be included since the areas of brain stained in this condition were similar to those affected in Wilson's disease! I imagine that both authors would have been pleased that this inclusion avoided the editorial censor since in 1926 Dr Wyllie was transferring from adult neurology via paediatric pathology to a distinguished career in child guidance, while Dr Poynton, whose career achievements included being a stylish middle order batsman for Somerset Cricket Club and BPA President, had just published a case report on Wilson's disease.

Then, the brain damage in both was attributed to hepatic toxins. What has changed? In 1948 the association between excessive copper accumulation and tissue damage in Wilson's disease was established. Three years later effective chelation treatment was introduced. The hepatic mode of presentation of the disease without neurological abnormality was emphasised in 1957.[1] In 1986 delay in diagnosis in children is very frequent. Nearly 50% of those diagnosed at King's College Hospital are referred late with liver disease so advanced that they die in spite of chelation treatment. Liver transplantation, which will correct the metabolic abnormality, can save these children, but donor livers are rarely available. The role of unconjugated hyperbilirubinaemia in the pathogenesis of kernicterus is well established. How to determine the precise risk of kernicterus in the individual infant still eludes us.

Banti's anaemia, a concept of primary splenic disorder releasing toxins that cause cirrhosis, continued to have support until the 1950s when radiological, haemodynamic, and particularly histological studies confirmed that the primary disorder was portal vein obstruction or, more commonly, some form of liver damage, particularly chronic hepatitis. In the '50s corticosteroid responsive autoimmune chronic active hepatitis was gradually defined. The concept of chronic hepatitis and multilobular cirrhosis remained confused until in 1965 Blumberg identified a serological marker for hepatitis B infection. Hepatitis B affects up to 90% in the first six years of life in some parts of Africa. At least 10% develop chronic hepatitis. More worryingly, viral deoxyribonucleic acid (DNA) becomes integrated with host DNA. Liver cancer may ensue. There is as yet no treatment for hepatitis B infection. Molecular biologists have used recombinant DNA technology to produce from yeasts a vaccine that is immunogenic.[2] Given the correct priorities its use could lead to the elimination of this, the last important viral infection, which could be prevented by immunisation. Hepatitis A virus in contrast causes only acute hepatitis.

In considering biliary cirrhosis biliary atresia predictably had a prominent part. Death from a bleeding diathesis by 8 weeks of age was the norm. By 1940, it was clearly established that vitamin K was important in preventing haemorrhagic disease of the newborn and in that associated with cholestatic disorders. Sadly, the prothrombin time is still overlooked as an essential test in liver disease, and cholestatic babies still develop intracranial bleeding that could have been prevented by vitamin K.

Given the 10 year survival of 90% after surgical correction of biliary atresia in the first eight weeks of life, it is equally disappointing that in the United Kingdom referral is usually later.[3] Paediatricians do not see all babies with jaundice at 4 weeks of age. Diagnosis is therefore delayed.

In considering intrahepatic disorders to be distinguished from biliary atresia familial cases were emphasised. In 1926 the only well characterised disorder was infantile polycystic disease. Today, there are over 20. The most frequent is α_1 antitrypsin deficiency, first associated with liver disease in 1968.

In 1986 not only is the complete chemical structure of this glycoprotein and the genetic composition of its variants fully established, but with the wonders of DNA technology mammalian cells may now be modified to synthesise the complete glycoprotein.[4] This opens up the way to α_1 antitrypsin replacement therapy and antenatal diagnosis by analysis of DNA in chorionic villi.

The review completed, the authors returned to the undiagnosed cases. Two are siblings with photographs and features we would now recognise as being typical of glycogen storage disease, a condition defined clinically and pathologically in 1929. Now there are 12 different enzyme defects in glycogen storage disease, some of which are further subdivided into distinct pathophysiological variants with genetic, prognostic, and therapeutic implications.[5] In the remaining two cases further laboratory investigations, including percutaneous liver biopsy, using the Menghini technique introduced in 1958, would also be required.

The last 60 years has seen considerable advances in the management of liver disease in children. There are still many poorly characterised disorders and much remains to be discovered about causes, pathogenesis, and treatment. With the exciting advances now occurring in cellular and molecular biology, we have an unrivalled opportunity to increase our understanding of these processes and to provide more effective help for our patients. We must strive to bridge the gap between the work of the basic scientist and clinical problems. Paediatric hepatology is still an emergent speciality. The opportunities for research orientated paediatric hepatologists have never been greater. The conclusion of Doctors Wyllie and Poynton that 'It is often impossible to be certain either of the nature of the cirrhosis or of its origin' still applies!

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FOUR CASES of IMMUNO-TRANSFUSION with remarks on the Method

BY

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AND

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Immuno-transfusion is a comparatively recent extension of treatment by blood transfusion and the following case seems worth recording as an example of recovery from a desperate illness after other methods had apparently failed.

Summary and Conclusion.

1. Four cases of proved septicæmia treated by immuno-transfusion with one recovery and three deaths are described.
2. The success occurred in a pneumococcal septicæmia consequent upon empyema and seems attributable to the transfusion.
3. All four cases had previously undergone surgical operations.
4. Immuno-transfusion, though by no means a certain cure for septicæmia, offers a hopeful line of treatment in some cases.

Commentary

C A CLARKE

Clinical findings

The successful case was that of a boy aged 2 who had a left sided pneumococcal empyema with a positive blood culture.[1] A pneumococcal vaccine was prepared from the patient's blood, and a dose of 1000 million organisms was injected into his father; five hours later 350 cc of the father's blood was removed, defibrinated, and injected into the child's median basilic vein. 'His temperature and pulse fell immediately and by the next morning he was much better . . .'. Six months later 'his general condition, except for a little bronchitis, remained excellent'.

Cases 2, 3, and 4 all died, one from *Staphylococcus aureus* infection after osteomyelitis of the femur and two from streptococcal blood stream infections.

I was not particularly impressed by the reason given for the recovery of case 1. Firstly, in the month after the immunotransfusion his temperature was never completely normal; secondly, he had another attack of orchitis similar to an earlier episode; and, thirdly, a small empyema developed on the right side. Again he had already survived two and a half months before the immunotransfusion, and pneumococcal infections tend to be less lethal than those caused by the *Staphylococcus* or *Streptococcus*. But still, he survived, and I wonder if he is still alive. Can he be traced, or does the Data Protection Act protect his data from follow up? It would be interesting to know his present antibody state.

The results in two of the many references that I looked up are contradictory. Kilgore is all gloom and doom.[2] He reports three cases of *Streptococcus viridans* endocarditis: 'All three were 'improved' in their own and families' opinion, but in none could I see any beneficial effect other than temporary relief of anaemia and the psychic uplift to be expected from any strange and elaborate treatment'.

Greenslade on the other hand describes an orphan girl aged 6 who in one week had two extensive mastoid operations and one operation for lateral sinus thrombosis.[3] Her chances looked hopeless, but after immunotransfusion from a convent sister donor her condition improved immediately and she made a complete recovery. His other two cases were almost as dramatic, both recovering.

The scientific validity of immunotransfusion

Wright *et al*[4] thought that the critical time for the patient to be transfused was about five hours after the donor had been injected; this was based on studying the number of colonies of bacteria surviving in vitro in the donor's blood before and after his vaccination. They also found that the effect was non-specific and surmised that the vaccination had simply stimulated the donor's phagocytes (opsonisation) and that these were much more effective in destroying the bacteria than were the patient's own worn out cells.[4]

I took advice on Wright's hypothesis and the experts chorused: 'In no way . . .'—and who was I to judge? But I had a theory. Had the donors been 'sensibilised' by the patient—after all, they lived under the same roof? And I was reminded of the 'little old man' who was one of our Rh negative volunteers. He had no overt rhesus antibodies, but when we injected him with Rh positive cells the antibody appeared within 24 hours. On taking a proper history, we then found that he had had a blood transfusion in the first world war. 'Sensibilisation' surely?

The mystery to me is why Wright needed his particular opsonin theory; he was aware of the way antibodies were formed and knew that one could have donor panels for use in seriously ill patients and that therefore the time factor need not be critical. He seems to have thought, however, that these antibodies could not be specifically tested against the patient, whereas his stimulated phagocytes could.

Sensibilisation—or not—of the donor would account for the 'hit or miss' results, but why the 100% failure rate in subacute bacterial endocarditis? I suspect that the formation of immune complexes[5] provides the answer; these are highly likely to occur in subacute bacterial endocarditis and were responsible for the fatal outcome.

Obviously, immunotransfusion took a back seat with the coming of antibiotics, but it is now coming into favour again in the form of gammaglobulin infusions, particularly for viral diseases (McCarthy K. Personal communication) against which antibiotics are not yet well developed. Donor panels are available, and the technique seems particularly effective in viral diseases that are predisposed to by immunoincompetence.

But treating viral diseases is not new. In the 1930s a child in Great Ormond Street was extremely ill with generalised vaccinia. Alan Moncrieff contacted the army at Aldershot and obtained plasma from recently vaccinated army recruits. This was transfused into the child and resulted in rapid healing of its condition (Stroud CE. Personal communication).

Specific gammaglobulin infusions are also being advocated in severe bacterial infections where, increasingly, the organisms are resistant to antibiotics.

So did Almroth get it right? In some ways 'No' and in others 'Yes', but he was certainly a proper doctor for my heart warms to his views on statistics.[6]

'The statistician has done his very best to persuade the world that there is only one way, that being the statistical method, by which the efficacy of a therapeutic method can be scientifically put to the test . . .', but this, because of heterogeneity, 'is almost invariably fallacious'. Fortunately, there are 'non-statistical methods by which efficacy can be tested—words graphic enough to depict to the reader the desperate condition of the patient when treatment was initiated, and the resurrectional change that followed . . .'.

Sixty years on we have a similar problem in reverse, relating to plasmapheresis in rhesus immunised women.[7] Sometimes it works and sometimes it doesn't, but no two cases are the same. For example, the antibody concentrations may be transiently reduced, but because of an antigenic stimulus acquired in the course of treatment there is a rebound effect. Again, more recently, there is evidence of a factor that normally inhibits antibody production and this may be removed by plasma exchange. The statisticians call for a properly controlled trial, but they are crying for the moon—read the case histories and see.

Envoi

G B Shaw and Almroth were friends and sparring partners, and phagocytes figure large in 'The Doctor's Dilemma'.

I wonder if there is anything in the five hour story? Almroth and his followers were remarkably sure about it. Why not try it in AIDS? — in vitro, of course, unless a non-specific stimulus would do the trick.

I recently met Leonard Colebrook's great nephew at the 'BODY' tree planting ceremony at Cambridge. He is a general practitioner in Bedford and knows all about his ancestor.

I am most grateful to Professor Kevin McCarthy and Dr Nevin Hughes-Jones for their helpful advice and to Professor CE Stroud for his vaccinia anecdote.

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(Bernard Schlesinger was a founder member of the British Paediatric Association and became its President in 1953–54.)

(Sir Cyril Clarke, a former member of the Archives Editorial Committee, was awarded the James Spence Medal in 1973 in recognition of his contribution to the prevention of rhesus haemolytic disease of the newborn. He is a past president of the Royal College of Physicians of London.)

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An Investigation of
SCLEREMA NEONATORUM; with Special Reference to the Chemistry of the Subcutaneous Tissues.
(Part I.)

BY

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WITH

A HISTOLOGICAL REPORT

BY

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Introduction.

Sclerema neonatorum is a rare but interesting condition peculiar to infants. The extraordinary confusion that has existed in the past in . . . .

Commentary

M L CHISWICK

Chaussier coined the term 'sclérème' around 1815 to describe hardening of the skin in the newborn, and by the end of that century the expression 'sclerema neonatorum' was in general use. Much earlier descriptions of this disorder appear under a variety of names. One might think that sufficient time had elapsed for us to have learned everything there was to know about the pathogenesis of this disorder and that the subject was now closed. Not so—because we have been hampered by confused terminology. Only a few reports claiming to be about sclerema neonatorum refer to that disease as we know it today.

Harrison and McNee's meticulously researched account of the histology and chemistry of subcutaneous fat in five infants with 'sclerema neonatorum' is really about subcutaneous fat necrosis.[1] The infants were admitted to hospital between 4 days and 5 months of age. In all but one, firm swellings over the buttocks, back, shoulders, neck, and thighs, with an overlying purplish discoloration of the skin, had been observed during the first week of life. The localised and well defined nature of the swellings, which in some infants discharged a milky fluid, is in contrast to sclerema neonatorum, which is a diffuse hardening.

Harrison and McNee observed that in affected areas the fibrous trabeculae between fat lobules were thickened; acicular crystals of neutral fats were seen 'lying in bunches like sheaves of corn' around fat lobules; multinucleated giant cells were prominent; and calcium salts were seen to form a coating on some of the fat cells. Biochemical changes in the subcutaneous fat were not striking and consisted of a raised melting point and a questionable reduction in olein content. The authors correctly suggested that changes in fat metabolism were unlikely to be the primary event but instead were probably secondary to inflammation.

In a forthright presentation to a meeting of the Royal Society of Medicine at Brighton in 1959[2] Elliott emphasised the difference between subcutaneous fat necrosis and sclerema neonatorum and distinguished both of them from 'neonatal cold injury'—the condition that Trevor Mann and he had drawn attention to in the *Lancet* two years previously.[3] Elliott emphasised that there was no need to postulate that the pathogenesis of subcutaneous fat necrosis depended on a chemical change in the fat itself. Yet, in a frequently cited paper based on one patient, Horsfield and Yardley, in 1965, propagated the notion that 'sclerema neonatorum' (in reality subcutaneous fat necrosis) might be a generalised disorder of fatty acid metabolism manifest by a raised ratio of saturated:unsaturated fatty acids locally in subcutaneous fat epidermis, and dermis.[4]

If we accept that subcutaneous fat necrosis is a localised chronic inflammatory response to trauma then what is the nature of the trauma? Today we speculate intrauterine compression injury. All sorts of things, which fortunately we cannot see, happen in the womb—so we are on strong ground here. Yet it is curious that whereas now most affected infants are healthy and have an excellent prognosis, 60 years ago it was not unusual for affected infants to be chronically ill with failure to thrive, fever, diarrhoea, and vomiting. Indeed, four of the five cases described by Harrison and McNee died. There are a number of plausible reasons for this difference. Firstly, overt birth trauma and presumably intrauterine compression injuries were more common then, and subcutaneous fat necrosis might merely have been incidental to the illness that led to admission to hospital. I note, for example, that the necropsy findings in one of Harrison and McNee's cases almost certainly describes the appearance of congenital hypertrophic pyloric stenosis. Secondly, infective diarrhoea and failure to thrive were so common one wonders whether affected infants were drawn from the poor community where lack of warmth in the home was compensated for by overtight swaddling. Thirdly, there is the possibility that a proportion of infants were the victims of physical abuse, with associated failure to thrive and chronic ill health. The purplish discoloration overlying lesions on the limbs would have been attributed to the fat necrosis rather than to bruising.

Sclerema neonatorum has a quite different appearance, and most paediatricians are familiar with the ominous sight of an ill preterm baby whose skin takes on a waxy pallor associated with a progressive induration and coldness. Sepsis or massive periventricular haemorrhage are common underlying conditions and most affected infants die.

In 1722 Usenbenz, a German physician, published 'Eighth month live birth, cold and rigid'[5]—a paper that the present editors of the Archives would have warmed to because of its concise title. Usenbenz described a soldier's wife who gave birth at eight months to a baby girl at a hospital, in Ulm. The girl was extraordinarily cold and hard, and her cheeks could not be indented even with strong pressure. He likened her entire body to 'a piece of smoked meat'. In spite of wrapping her in warm linen and warming her in front of the fire, she remained 'stiff from head to heel . . . unresponsive and immobile, without the least cry having been heard'.

Underwood drew attention to this disorder in the first edition of his paediatric textbook in 1784 when he likened the condition to 'hydebound' in quadrupeds.[6] The disorder was commonly observed in European hospitals at the end of the 18th and beginning of the 19th centuries. The French published works refer to 'enfans durs' or 'enfans gelés', thus providing the rationale for one form of treatment, which was to place the infant in a warm bath containing two or three litres of wine, followed by massaging the infant's body with brandy[7]—which was no doubt pleasurable even if not effective.

Some of the infants referred to in the historical publications were probably not examples of sclerema neonatorum but were suffering instead from cold injury. Observing how sclerema neonatorum occurs today, I am impressed by how the rectal temperature often remains near normal while the skin temperature rapidly falls. The widening rectal–skin temperature gradient is associated with poor capillary return on blanching the skin and progressive pallor as the skin becomes indurated. All this in spite of the use of plasma expanders.

The pathogenesis of sclerema neonatorum is still unclear. The histology of the subcutaneous fat is quite unlike the chronic inflammatory picture described by Harrison and McNee. In fact, there is very little to see apart from thickened trabeculae between fat cells.

Sclerema neonatorum probably does reflect a change in the chemical composition and physical properties of subcutaneous fat, but accounts of the biochemistry of this condition are of limited value because they are generally based on isolated case reports and poorly matched controls. The ratio of saturated:unsaturated fatty acids is increased in the subcutaneous fat of preterm infants, and it would seem that this feature is even more pronounced in infants with sclerema neonatorum.

Earlier reports of sclerema neonatorum suggested that it was as common in term infants as in preterm ones—the latter usually presenting within a day or two of birth. Now the condition is virtually confined to our 'new population' of extremely preterm infants in whom I have the impression that it presents later—sometimes after the second week—just when hopes for survival are being raised. By this time, the composition of subcutaneous fat has had time to be influenced by the nature of the infant's diet, be that parenteral nutrition or milk. Bearing in mind that we have a new population of patients and also that changes have occurred in the nutritional care of preterm babies, re-evaluation of the biochemistry of subcutaneous fat in sclerematous infants and extremely preterm controls of the same postnatal age is long overdue.

We might also take the opportunity to rethink this interesting disorder in terms of the metabolic vulnerability of polyunsaturated fatty acids. Are these fatty acids sheltered and protected in the subcutaneous layer, or are they vulnerable to attack by free radicals? Peripheral circulatory failure and sepsis are circumstances that probably promote the production of free radicals. Might sclerema reflect structural changes in fat cell membranes brought about by free radical damage? Only a minority of critically ill preterm babies become sclerematous, and in them are the scales tipped by a relatively deficient 'antioxidant system'? Someone had better do the work before sclerema neonatorum becomes extinct.

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THE SPECIAL SCHOOLS OF LONDON.

BY

F. C. SHRUBSALL, M.D.

Although, unquestionably to the ailing child, the restoration of health and relief from crippling conditions are of supreme importance, experience has shown that when the necessary measures are spread over a period of years under such conditions as to limit the possibilities of education, still more if they are such as altogether to prevent formal education, the child is unduly handicapped on reaching the employable age. This difficulty became obvious so soon as universal elementary education was made the law of the land.

From the first the by-laws of the various school boards laid it down that ill-health was a reasonable cause of absence from school; but . . . .

Commentary

N GORDON

In the introduction Dr Shrubsall starts by saying that when the necessary measures to restore health and relieve crippling conditions are spread over a period of years, under such conditions as to limit the possibilities of education, the child will be unduly handicapped on reaching an employable age. In 1893 an Act was passed allowing provision for special education for blind and deaf children and in 1899 for those crippled, epileptic, or mentally defective. To start with this was on a voluntary basis, and it was not until after the first world war that it became a duty in all areas of England and Wales. A few years before 1926 hospital schools had been established for long stay patients.

At that time the London County Council provided special education for children who were blind, deaf, or physically or mentally defective and for stammerers and places in residential schools for those with epilepsy. The Council's medical officers had to examine all such children and visit the schools from time to time; decisions could then be enforced by law. Dr Shrubsall describes the groups and school facilities as follows.

The blind, partially blind, and myopic

A blind child is one who is too blind to read the ordinary school books used by children. The instruction in the schools for the blind includes the teaching of braille and suitable forms of handwork occupations. At the age of 12 suitable children are transferred to residential schools for special trade training until the end of the school term in which they attain the age of 16. Children affected with myopia leave school at 14. They are naturally studious and more prone to read out of school, which should be discouraged unless from suitable type. (Considering that the association of myopia and the higher levels of intelligence has been recognised for so long, this might have received more study than it has.)

The deaf

A deaf child is one who is too deaf to be taught in a class of hearing children in an elementary school. Deaf children may be admitted to school at the age of 5 but this cannot be enforced by law until the age of 7. In such schools oral methods of instruction are used, special attention being paid to lip reading and pronunciation. At the age of 12 suitable children are transferred from schools for the deaf to residential schools for special trade training until the age of 16. Special classes are provided for those who are not severely deaf, and as soon as they have acquired powers of lip reading they are marked for transfer to an ordinary school. There is a special school in Penn for 'the few oral failures' and for children who are deaf and also blind or mentally defective. A nurse attends all these schools to treat discharging ears. (No mention is made of any controversy between oral methods and signing.)

Physically defective

The usual ground for admission is some cause of crippling, or some organic disease, that renders attendance at an ordinary school disadvantageous but does not prevent a child being educated in a small class under constant medical and surgical supervision. An ambulance is provided for children who live at a distance and are unable to use public transport. Provision is made for a certain number of recumbent children, and a nurse is in constant attendance. The school is visited by the school doctor at least every four weeks and periodic visits are made by an orthopaedic surgeon. Attendance can be enforced to the age of 16, but when feasible the child is transferred back to an ordinary school.

The constant supervision in schools for the physically defective provides a valuable link with the hospital, as children can obtain further advice at the onset of any untoward occurrence. They are fully occupied under supervision so that the concern expressed by some that they will be turned into invalids is unjustifiable. Most children suffer from paralysis, quiescent tuberculosis of bones or joints, congenital deformities, and heart disease. Children with epilepsy are not admitted.

Older children are transferred to separate schools for trade instruction, adapted to their physical defects and to the possibilities of their obtaining local employment.

Open air schools

These are provided for children from the age of 8. One type is for debilitated and anaemic children and those liable to tuberculosis and another for those with definite pulmonary tuberculosis or tuberculous glands.

Epileptic children

There are arrangements for children who suffer from chronic epilepsy of such a degree as to make them unfit to attend an ordinary school but whose mental state allows them to derive benefit from education in residential epileptic colony schools, if they are between the age of 7 and 16. To derive this benefit children should be sent at a relatively early age. Physicians may postpone a recommendation for residential treatment and keep the children for considerable periods out of school, which is not always desirable.

Stammering classes

Arrangements exist for children of 8 years and upwards to attend for a course of three months at classes taken by specially trained teachers.

Mentally defective children

Before a child attending an ordinary school is proposed for admission to a special school he is seen by the school doctor and arrangements made to secure treatment for any defect such as poor vision, partial deafness, and mouth breathing. Then the child is examined by special medical officers. Generally, the children admitted are those whose mental age is estimated as less than three quarters of the normal. In these schools classes are small with specially trained teachers and a special curriculum, with separate schools for trade instruction for the older children. When possible the child is transferred back to normal school. At 15½ years all children are reconsidered, and those deemed to need institutional treatment due to lack of intelligence are referred for care under the Mental Deficiency Act. Those who can cope receive after care until the age of 18.

Such children, if kept in ordinary schools, may fall further and further behind due to a sense of inferiority. If they are transferred to a special class, however, they learn they may be of use in the world and receive praise instead of blame, to the benefit of their self respect.

Dr Shrubsall sums up the aims of the special schools as to obtain the best possible combination of treatment and education and to secure the utmost cooperation between the school medical service, private practitioners (GPs), and hospital physicians and surgeons. The staff at special schools today surely have the same aims. It is perhaps surprising that there were so many provisions of this kind 60 years ago, although London may have been unique. No mention is made of numbers except that there were 4432 children on the rolls of schools for the physically defective out of a total school population of 697 882.

The problem of children attending special schools in 1986 will have changed in many ways, but there are several basic truths in this paper. Changes are on their way but will they be advantageous to all? Integration of handicapped children into normal schools seems to be a laudable objective and may benefit many of them but not all; and then only if schools are given the extra resources to cope with the extra problems that will undoubtedly arise. It will certainly not work if it is regarded as a money saving exercise. Also there are dangers in generalisations. There are some children, not necessarily those with the severest handicap, who need the extra support, both in and out of the classroom, that only special schools can provide. I cannot express it more adequately than Dr Shrubsall.

In the same volume there is a short paper (pp 230–1) by Dr Dingwall Fordyce of the Royal Liverpool Children's Hospital. He makes the point 'that Intelligence Tests are valuable for the practitioner, particularly in assessing children with physical defects who suffer from long-continued or recurrent ailments, and for those with scholastic retardation and character anomalies.

'The intelligence quotient is, at best, one aid to a decision affecting the individual, but it is an important one; and combined with scholastic tests often gives valuable information as to aetiology, prognosis and desirable procedure.'

(Neil Gordon, one of the founders of paediatric neurology in Britain, was awarded the highest distinction of the British Paediatric Association, the James Spence Medal, in 1985. For most of his career he has worked in Manchester.)

Archives of Disease in Childhood, 1986, **61,** 952–953

LAMBLIASIS AS A CAUSE OF CHRONIC ENTERITIS IN CHILDREN.

BY

REGINALD MILLER, M.D., F.R.C.P.

(From Paddington Green Children's Hospital.)

Intestinal infections due to the flagellate, lamblia intestinalis, attracted attention in England in the early years of the war when the disease first reached this country from the Eastern fronts. Since 1916, with the exception of Clifford Dobell's report(1), hardly any further reference to the disease has been made in English medical literature. I can find no clinical study of the infection published in this country though many papers on the subject have appeared in America.

This paper is based upon the study of 23 children infected with lamblia and has been largely written without previous reference to the publications of other observers. The conclusions reached are (1) that the infection is now by no means a rarity in hospital practice amongst children; (2) that it produces a chronic enteritis; (3) that the resultant diarrhœa is often severe enough to cause the subjects of the disease to be considerably below their proper weight, and occasionally will produce retarded development and diminution of growth, suggesting that in lambliasis we have a further possible cause of infantilism of the enteritic type; (4) that even in children true "carriers" may be found, infected with lamblia, but without symptoms.

Commentary

A S McNEISH AND I W BOOTH

This paper, by the first joint editor of *Archives,* gives a brief account of 23 children with chronic diarrhoea and suboptimal growth in whom *Giardia lamblia* cysts were found in the stools. The text moves from factual description to generalised statements about 'lamblia' infection, emphasising that the clinical picture can vary from the asymptomatic carrier state to 'chronic enteritis with infantilism of the enteric type.'

From a modern standpoint this paper has three* defects. Firstly, Miller had no test to exclude coeliac disease, 'which lamblia may resemble more than any other.' Secondly, he could not test the clinical result of treatment, because no effective treatment against giardia was available. Third, giardia was common in the 1920s—the survey quoted in the paper suggested a carrier rate in England of 18–27%.[1] The finding of the parasite in some of Miller's patients may have been coincidental.

And yet Miller may have been right. *G. lamblia* is endemic throughout the world and is spread by faecal–oral contamination, with the added possibility of animal reservoirs of infection.[2] Fifty per cent of all infection may be asymptomatic. The active clinical picture is of acute diarrhoea, leading to chronic diarrhoea in a variable proportion.

Attachment of the parasite to the mucosa of the small intestine is regarded as a crucial step in

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*There is a fourth defect. Miller's concern for accuracy of reference would not satisfy a modern editor. The reference to Dobell is in fact an editorial in the *British Medical Journal*, which quotes Medical Research Council Special Report Series No 59 (written by C Dobell *et al*), 'A report on the occurrence of intestinal protozoa in the inhabitants of Britain.'

pathogenesis. The exact mechanisms by which diarrhoea and malabsorption result are incompletely understood, but there is evidence for both mucosal and luminal factors. Enterocyte damage, mucosal inflammation, and on occasion direct invasion of the mucosa have been shown by light and electron microscopy, with the severest lesions being found in association with immunodeficiency.[3]

Intestinal bacterial overgrowth, inhibition of lipolysis, pancreatic insufficiency, and, rarely, inflammation of the bile ducts have all been found clinically or experimentally.

The evidence that infection with the parasite can interfere with growth comes from experimental infection in young animals.[4] [5] Analysis of the limited retrospective and cross-sectional data in children suggests that *G. lamblia* can interfere with linear growth and often causes faltering in weight gain or even weight loss.[6] The unique community based longitudinal studies by Mata of the children of Santa Maria Cauqué support this view.[7]

Why is there such a variation in the clinical picture? Differences in strain virulence and in host (immunological) susceptibility are proposed but are largely unexplored. Sixty years after Miller, there is much work to be done.

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(Further information about Reginald Miller, who was the inaugural editor, is given on page 979).

(A S McNeish is Professor of Paediatrics and Child Health in the University of Birmingham and recently completed a five year term of office on our Editorial Committee. I W Booth is Senior Lecturer in Paediatrics and Child Health in the University of Birmingham.)

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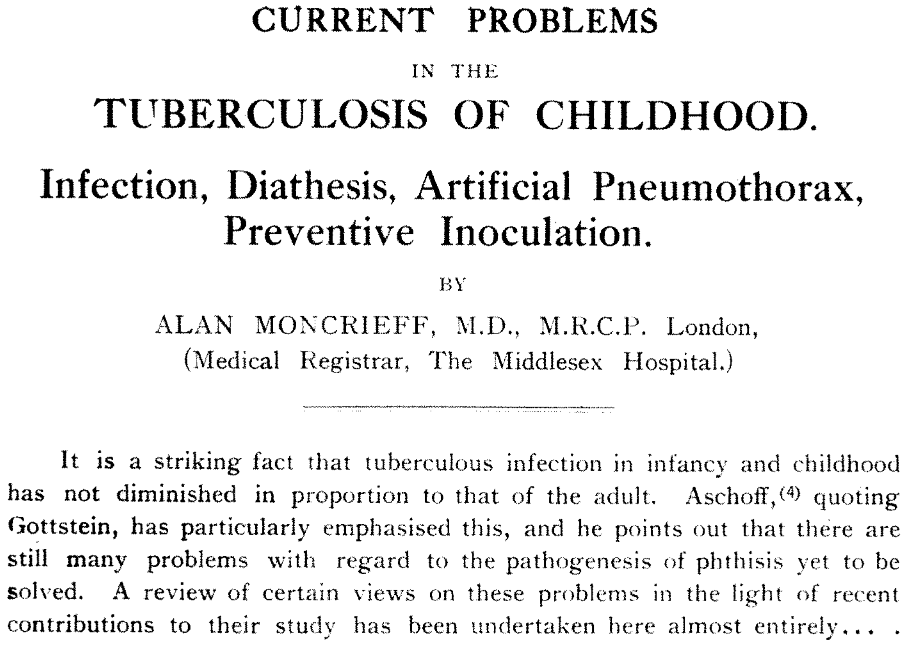

CURRENT PROBLEMS
IN THE
TUBERCULOSIS OF CHILDHOOD.
Infection, Diathesis, Artificial Pneumothorax, Preventive Inoculation.

BY

ALAN MONCRIEFF, M.D., M.R.C.P. London,
(Medical Registrar, The Middlesex Hospital.)

It is a striking fact that tuberculous infection in infancy and childhood has not diminished in proportion to that of the adult. Aschoff,(4) quoting Gottstein, has particularly emphasised this, and he points out that there are still many problems with regard to the pathogenesis of phthisis yet to be solved. A review of certain views on these problems in the light of recent contributions to their study has been undertaken here almost entirely... .

The paper is based on the author's MD thesis and is a review of certain aspects in childhood tuberculosis.

Commentary

B D BOWER

Summary

Childhood pulmonary infection is generally accepted as being caused by the human tubercle bacillus. The evidence from sputum and bronchial gland cultures is overwhelming; in Japan, where cow's milk is not used in infant feeding, pulmonary tuberculosis is as common as in the United Kingdom. The portal of entry is less certain. Suggestive evidence exists for the intestinal, the pharyngeal, and even the conjunctival routes, but that for the 'direct aerogenous' route is most convincing. Ghon, in particular, has shown the subpleural focus with infection of the draining lymph glands in 95% of 184 autopsies.[1]

The existence of an inherited tuberculous diathesis is still debated, but most of the evidence in its favour can be explained on another basis—that is, the amount of contact with infected individuals, which means the dose of bacilli inhaled. The striking results of separating newborn infants from their tuberculous mothers by comparison with those not so managed support this.

In the treatment of children with pulmonary tuberculosis artificial pneumothorax is used in France and Germany, but not in Britain. Results from several hundred children of all ages treated for up to four years are given and suggest that it can prolong survival, but the author evidently has no first hand experience of the method.

Prophylactic inoculation. Calmette and his school have produced an avirulent strain of the tubercle bacillus, 'Bilié—Calmette—Guérin', by 230 successive cultures.[2] This has been given orally to over 2000 newborns whose mothers have active tuberculosis and have refused to be separated from their infants. No tuberculosis has been detected in the infants when followed up, and no death was due to tuberculosis. In Britain various tuberculins and dead vaccines from attenuated bovine bacilli are being given by injection to child contacts, with some initial promise.

Discussion

It is difficult for most paediatricians working in Britain today to imagine the clinical scene in the wards or outpatient clinics in 1926. Tuberculosis, still a contender for the title of 'captain of the men of death' with an annual death rate (at all ages) of 80 per 100 000 population, killed relatively slowly even in children. It therefore formed a large part of clinical medicine and surgery at all ages. Treatment was by indirect means—improved nutrition, general and local rest—and was slow in results when it worked at all. (Incidentally, why was artificial pneumothorax never a popular treatment for children in Britain in contrast to Europe?) Alan Moncrieff, then a medical registrar, knew the essential facts about the aetiology, pathology, and spread of childhood pulmonary tuberculosis; but he and his colleagues were impotent to influence its course. It was not until more than 20 years later that effective antibiotics became available and transformed the clinical and epidemiological scene.

Prevention, however, was receiving attention 60 years ago, particularly in France, and it is interesting to see that BCG was in existence and undergoing clinical trial at that time. It was first produced in a wooden shed in Lille in 1906, but it was not used to any extent in Britain until the 1950s. A freeze dried vaccine produced in this country was convenient to distribute and use and was soon accepted as effective. But it was the arrival of effective antibiotics and the organisation of case and contact detection nationally as well as locally that reduced the disease to its present relatively trivial proportions (annual notification rate of 12·2 per 100 000 for England in 1983 for all ages,[3] and negligible mortality).

On a global scale it is far from trivial, and in Britain the results of the large scale immigration of Asians in the first two postwar decades still remind us of this. The incidence in Asians of all ages is still 25 times greater than in whites.[3] For children the annual notification rates seven years ago were (per 100 000): for Indians 90; for Pakistanis and Bangladeshis 130; and for whites seven;[4] and the proportions are likely to be similar today. The reservoir of carriers in older adults and the return visits of children to their country of origin will prevent a rapid fall in the rate of infection of Asian children in the near future. In spite of the much greater risk to this group, however, it is important to recognise that in Britain white children constitute the largest group of newly infected cases (50% of the total[4]).

In a treatable disease diagnosis is particularly important. In childhood tuberculosis today early diagnosis may make the difference between complete normality and survival with severe handicap, for instance in meningitis. Yet because of its present rarity, diagnosis is more likely to be delayed in 1986 than it would have been in 1926. (Is it significant that only 15% of cases in 1977–78 were notified by paediatricians, while 73% were notified by chest physicians?[4]). Not only must the possibility of tuberculosis be considered when an Asian child presents with undramatic symptoms, but it must be realised that in Asian children the presentation is more likely to be with extrapulmonary symptoms, which may be misleading if the usual description of primary tuberculosis given in Western textbooks is considered typical. One must remember, however, that in Britain today the clinician is at least as likely to encounter tuberculosis in a white child.

Prevention must continue to concentrate on the Asian communities. After the diagnosis and treatment of open adult cases, contact tracing and chemoprophylaxis of children are the most important activities. BCG has been useful as a general preventative measure. But the point has now been reached where 2500 immunisations are required to prevent one infection. At present offered to 13 year olds of all racial origins, it may soon be sensible to offer it selectively, for instance to Asian newborns and children entering Britain.

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(Information about the author, Sir Alan Moncrieff, who later became Editor of the *Archives*, is given on page 980.)

(Brian Bower, who is a Consultant Paediatrician at the John Radcliffe Hospital, Oxford, is a past member of our Editorial Committee.)

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NEPHRITIS IN CHILDHOOD

BY

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for the Medical Research Council.)

The investigations upon which this paper is based were undertaken primarily to examine the practical value of the so-called "renal efficiency tests" in children. Cases of kidney disease admitted to one of the medical wards of the Royal Liverpool Children's Hospital were systematically examined, and the results have been analysed. This has necessitated a general survey of kidney diseases, and of the special peculiarities of these diseases in children. So far as possible, the pathological and clinical aspects have been correlated in the classification adopted; and an attempt has been made to emphasise the necessity of taking a broad general view of each case studied.

The paper is sub-divided under the following headings:—

1. Classification of nephropathies.
2. Methods of investigation.
3. Description of cases studied.
    - (A) Acute glomerulo-nephritis.
    - (B) Chronic glomerulo-nephritis.
    - (C) Diffuse tubular nephritis.
4. Pathological findings in diffuse tubular nephritis.
5. Treatment.
6. Summary and conclusions.
7. Bibliographical references.

Commentary

G C ARNEIL

The personality of Norman Capon, a man of wit and wisdom complementing perspicacity and pioneering thought, shines through this very early attempt to rationalise the approach to nephritis in children. One must remember this was during a time when streptococcal acute glomerulonephritis was common as was chronic, acute, and lethal sepsis, antedating by 10 years the use of Prontosil rubrum and by 20 years the widespread use of penicillin. His paper is neatly compartmentalised and is perhaps best considered in this way.

Classification of nephropathies heads the list and like every subsequent attempt falls between the Scylla of clinical findings and the Charybdis of pathological dogma, until then unchallenged as it was, de facto, the last word. It may be summarised as nephrotic syndrome, nephritic syndrome, and chronic renal failure—not a bad start even today. We have now passed the zenith of pathological influence, but the pressures imposed by needle biopsy, light microscopy, electron microscopy, and immunohistochemistry backed up by some outstandingly dominant personalities has stressed the patience of many paediatric nephrologists. The acceptance that similar lesions may result from differing insults and that pathologists are *not* always right, when biopsy examination is followed by clinical course, is restoring a more realistic balance. It is interesting to note that even then focal and interstitial nephritides were well recognised.

Methods of investigation are very revealing. Medical history, general examination, and urine examination were as good as or probably better than today. Serum biochemistry was crude and renal efficiency tests crude, lacking the sophistication and accuracy of modern clearance techniques and in particular isotope clearances.

The star item of the paper is, however, the inclusion of renal biopsy examinations, a very early example of this technique. That the concept of 'minimal change' stretches so far back is thanks to the vogue for bilateral renal decapsulation current at that time that led Campbell, a Glasgow surgeon reviewing his remarkably good results in the early 1920s, to suggest it was the anaesthetic and the operation (any operation!) that perhaps caused 50% to recover (stress of surgery equal to treatment with glucocorticosteroids?).

Description of cases studied is peppered with records of focal sepsis and systemic infection, which bring back memories to all paediatricians practising before the latter half of the 1940s.

Pathological findings are confused, with diffuse parenchymatous nephritis, diffuse interstitial nephritis, and other hoary old chestnuts confusing the issue. The morbid anatomy and histologies of a kidney decapsulated 86 days previously are of interest. The histology of glomeruli on biopsy examination reveal minimal changes, epithelial crescents, hyaline thrombus, and fibrous infiltration.

Treatment included dietetic (high energy and protein), diuretics (alkalis and urea) sadly lacking chlorathiazides (1950s), frusemide, and anti-aldosteronic agents. Elimination of septic foci contrast with prevention of viral infections and fear of fulminating gram negative septicaemia, which 'bugs' us today.

This is a refreshing leaf from history with an approach not dissimilar to that of today, albeit with less technology, pathological physiology, and no glucocorticosteroids, cyclophosphamide, or effective diuretics. If it is always true that we treat them, but God cures them, then at least we are able to help the Almighty a little more today as compared with 1926.

(Norman Capon was subsequently appointed to the Foundation Chair of Child Health in the University of Liverpool. He was a Founder member of the British Paediatric Association and was its President in 1951–52.)

(Gavin Arneil is Leonard Gow Lecturer and Professor of Child Health in Glasgow. He was the first Director General of the International Paediatric Nephrology Association. He is a past member of the Archives Editorial Committee and currently Editor of The Bulletin of the International Paediatric Association.)

Archives of Disease in Childhood, 1986, **61,** 958–959

CHRONIC ULCERATIVE COLITIS IN CHILDREN.

BY

GEOFFREY BOURNE, M.D., M.R.C.P.
(Physician to the East London Hospital for Children).

By ulcerative colitis is meant in this paper a chronic ulcerative condition of the colon, inflammatory in nature, and accompanied by frequent loose motions containing blood and mucus.

Other conditions associated with a minor degree of acute ulceration occasionally are found in infants and young children, but in them the acute enteritis, rather than the few ulcers associated with it, dominates the . . . .

Commentary

J A WALKER-SMITH

Dr Geoffrey Bourne, author of the article, was a physician on the staff of St Bartholomew's Hospital and King George's Hospital, Ilford. He was also physician to the East London Hospital for Children at Shadwell. He was regarded as a sound general physician with a special interest in children (Swain V. Personal communication). At St Bartholomew's Hospital he is best remembered for having established an electrocardiographic department. He was also an author, with several books to his credit, including one on politics. At St Bartholomew's Hospital until 1937 no full time paediatrician had been appointed, and so children were cared for by general physicians in adult wards. In 1942 the East London Hospital for Children at Shadwell amalgamated with the 'Queen's Hospital for Children', Hackney Road. For economic reasons Shadwell was eventually closed in 1962.[1]

Dr Bourne began his paper with what is still today a good clinical definition for the colitis of chronic inflammatory bowel disease. Naturally, he was unaware of the current distinction between ulcerative colitis and Crohn's colitis, as Crohn and his colleagues only went on to describe that disease for the first time some six years later in 1932.[2] What is remarkable, however, is that despite the fact that he was only reporting one child and reviewing the scanty world reports up to 1926 he firmly based his diagnosis upon two diagnostic criteria that have stood the test of time; firstly, clinical (diarrhoea with the presence of blood and mucus in the stools), and secondly, endoscopic—that is, sigmoidoscopic or proctoscopic (which he described as naked eye evidence of chronic disease).

He disregarded radiographic evidence alone, a view I would heartily endorse. Our current practice in the Paediatric Inflammatory Bowel Disease Clinic at St Bartholomew's Hospital is to use only endoscopy (colonoscopy and ileoscopy), with multiple biopsy for the diagnosis of colitis in childhood.[3] Endoscopically, Dr Bourne insisted on the presence of ulcerated colonic mucosa for precise diagnosis. In his case report Bourne described the presence of a number of small ulcers on sigmoidoscopy. Were these in fact what now would be called apthous ulcers? In fact, endoscopists now teach us, perhaps paradoxically, that such discrete ulceration is not a feature of ulcerative colitis but is characteristic of Crohn's disease. In ulcerative colitis there is typically a general granular appearance with increased friability and ulceration, which when present may be large and linear. Possibly, the case described was in fact one of Crohn's colitis or even, as the author mentions, a case of bilharziasis (schistosomiasis), acquired in Egypt because the patient responded to intravenous antimony tartrate.

Whatever the final diagnosis, in terms of current knowledge, the rarity of reported cases of ulcerative colitis—that is, chronic inflammatory bowel disease—in children up to 1926 is remarkable. At that time he could find only nine other what he described as well authenticated published cases in all the published reports world wide. He mentions seven other reports that may also include some cases of ulcerative colitis.

Nevertheless, it is truly remarkable that ulcerative colitis should have been so rarely reported in the published reports up to that time. In a recent review from St Bartholomew's Hospital 28 cases were described over 10 years,[2] and the reports on ulcerative colitis in children are now extensive. Why has this remarkable increase in the number of published reports occurred? Does it reflect a true increase in incidence in developed communities in recent years? The disease is still uncommon in children in developing communities—for example, in India—but when Indian children are born in Britain they also develop the disease.[5] Bourne, nor indeed his contemporaries, could have missed cases of chronic inflammatory bowel disease on any appreciable scale in the light of his clinical acumen and recognition of accurate diagnostic criteria and his knowledge of the disease in adults. Some environmental factors that have occurred in Western societies in the past 60 years must have been responsible for this change. It seems to be that an infectious agent, at least of the conventional type, is unlikely to account for this change, as in the last 60 years the environment has become progressively less hazardous microbiologically, with some notable exceptions of course, such as legionella and acquired immune deficiency syndrome (AIDS), that are related to special features of modern life. Could any such special features be involved here in childhood ulcerative colitis or must we look to some chemical or food related substance that triggers an inflammatory process in the colon that continues for immunopathological reasons? Bourne's clinical acumen and accurate description thus leads to fascinating speculation about the nature of this disease.

Ulcerative colitis is as much an enigma to us today as it was to Bourne. Therapeutically, we have a better armamentarium, and the techniques of surgery have greatly improved, with subtotal colectomy and ileostomy being effective treatment. Yet only the discovery of the precise cause and the development of more effective therapeutic techniques, preferably for prevention but also of effective and curative treatment, will do away with what can only be described as mutilating surgery. Complete eradication of this unpleasant disease can be our only goal.

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(John Walker-Smith is Professor of Paediatric Gastroenterology in the joint academic Department of Child Health for St Bartholomew's Hospital, The London Hospital, and Queen Elizabeth Hospital for Children. He served on the *Archives* Editorial Board 1976–80.)

Archives of Disease in Childhood, 1986, **61**, 960–961

CONGENITAL ABSENCE OF TIBIA.

BY

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AND

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I. Definition and Description
II. Clinical and Radiographic Features
III. Cases
IV. Diagnosis
V. Anatomical Descriptions
VI. Etiology
VII. Treatment
VIII. Conclusions
IX. Bibliography

Commentary

R W SMITHELLS

In this article an orthopaedic surgeon and his registrar report eight cases of a rare skeletal deformity, including five published previously. In an article running to 35 pages, including 12 photographs and eight detailed anatomical drawings, they describe the clinical, radiographic, and anatomical features and discuss aetiology and treatment. Their search of the published reports (which includes French, German, Italian, and American publications) revealed only 102 previously published cases, although the bibliography curiously omits a reference to Motta, who published a remarkable collection of 50 cases.[1] The discussion of aetiology refers to many theories and concludes that 'the cause is defective development of the mesoblast under an influence at present unknown, but not traumatic, mechanical, vascular or atavistic'.

Although only eight cases are here described, the paper brings out two points that larger series confirm—namely, (a) the frequency of additional defects, by no means all skeletal, and (b) the familial tendency in some cases. It is interesting to compare this paper with that of Kalamchi and Dawe (1985), who describe 21 children with congenital tibial deficiency seen over 30 years.[2] Despite reporting seven times as many new cases, the modern authors are constrained to four pages, including eight figures. They have no further light to shed on aetiology, they confirm the frequency of associated defects of many kinds (in 14 of 21 children), and share the views of Evans and Smith regarding treatment—namely, disarticulation at the knee and the fitting of a prosthesis for all but the mildest cases.

Interestingly, although several authors (including Evans and Smith) attribute the first reported case of congenital absence of the tibia to Otto (1841), no reference can be traced.*

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*The reference to the article by Otto has now been traced but is reported to make no mention of congenital absence of the tibia.

Biographical notes

(With acknowledgements to Lives of the Fellows of the Royal College of Surgeons of England and to Dr P F Smith, Librarian, Institute of Orthopaedics.)

Evan Laming Evans (1871–1945) CBE, FRCS, MD. Educated at Eastbourne College, Trinity College, Cambridge, and St Bartholomew's, London. Before settling on a career in orthopaedics he worked as assistant bacteriologist in the joint laboratory of the Royal Colleges of Physicians and Surgeons; as a general practitioner; and in the South African war as surgeon and physician, winning the Queen's medal with three clasps; and he wrote his MD thesis on typhoid fever. His consulting work included the Industrial Home for Crippled Boys, and he had a special interest in congenital dislocation of the hip.

Norman Ross Smith (1897–1965) MB, CHB (Sydney), FRCS. After graduating in Australia he came to London and worked at St Mary's, Guy's, St George's, the West London, and the Royal National Orthopaedic Hospitals before settling in Bournemouth. He was orthopaedic surgeon to the Shaftesbury Society's Victoria Home for Crippled Children. He was a stalwart supporter of the British Medical Association and was elected an Honorary Fellow shortly before his death.

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(R W Smithells is Professor of Paediatrics and Child Health in the University of Leeds. He is a regular contributor to the *Archives,* particularly on subjects relating to the prevention of congenital abnormalities.)

Archives of Disease in Childhood, 1986, **61**, 962–963

A CONTRIBUTION TO THE STUDY OF THE CAUSATION OF FŒTAL DEATH*

BY

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During the last few years, more attention has been paid to what has been, beforetime, a much neglected branch of pathology—the subject of fœtal and neo-natal death. Its importance is obvious. The yearly wastage of fœtal life assumes enormous proportions; nor is this all.

Commentary

J S WIGGLESWORTH

One hundred and sixty autopsies were performed at the Jessop Hospital for Women, Sheffield, as a consecutive series from March 1923 to March 1925, on infants who were stillborn or died in the first week of life. There were 117 stillbirths and 43 neonatal deaths.

Using a simple classification Dr Tingle considered that 17 (11%) of the cases were associated with maternal causes, mainly 'albuminuria' or eclampsia; 35 (22%) had placental causes, including placenta praevia, retroplacental haematoma, and infarction; and 129 (81%) had fetal causes, including trauma, infections, and anomalies. Twenty one cases were considered to have maternal or placental causes in addition to a fetal cause. Detailed analysis was restricted to the fetal causes. The major fetal cause of death was birth trauma, found in 105 (66%) of the infants. An unrecorded number of these cases were craniotomies; of the remainder, 58 (36% of all deaths) had tentorial tears. Intracranial haemorrhage was associated with the tears in 57 of the 58 cases. In 30 of the infants the bleeds were classified as 'much' in quantity, in 19 as 'moderate', and in eight as 'little'. Tentorial tears followed cephalic delivery in 30 infants, 17 of them with forceps, and followed breech delivery in 28, of whom 17 were delivered after version. Tentorial tears followed uncomplicated cephalic delivery at term in only two instances: other cases where forceps had not been applied were complicated by prematurity, contracted pelvis, or prolonged or precipitate labour. Prematurity was considered to be a major factor predisposing to dural tears, being present in 17 (29%) of the affected infants. The intracranial bleeding was recognised as originating from the extension of a tentorial tear into a sinus in five cases and from a torn vein of Galen in one. The origin of bleeding was obscure in the rest, but dissection of fixed fetal heads indicated that the haemorrhage had arisen from tributaries of the vein of Galen.

Two liveborn premature infants were found to have intraventricular haemorrhage extending through the third ventricle, aqueduct, and fourth ventricle. Eight cases of haemorrhage into one or both adrenals were recorded; seven of them had been delivered by the breech, and five had associated intracranial haemorrhage. Other sites of bleeding included the pleural cavities, the lung substance, the perirenal tissue, and the kidney.

Although trauma was clearly the dominant factor leading to haemorrhage, the possibility of haemorrhagic diathesis was investigated by measuring clotting times of newborn infants and their mothers. Four infants had delayed clotting times and died at ages from 12 hours to 7 days. Two of these were the premature infants with intraventricular haemorrhage: the others had multiple bleeding sites.

Infection was recognised in 14 cases, of whom nine had pneumonia. Organisms cultured from the lung included *Escherichia coli* or coliforms in seven cases, mixed staphylococcus and streptococcus in one case, and a pure growth of pneumococcus in one case where the mother also died of pneumococcal sepsis.

Of the 10 infants classed as showing fetal anomalies, four had cardiac anomalies, of whom two showed features of mongolism and two had other anomalies. Pulmonary atresia was the most common cardiac lesion. Other forms of anomaly included a case of achondroplasia, without family history, and an infant with generalised oedema. Histological examination of the latter infant revealed massive haemopoiesis in liver, spleen, and kidney, with excessive iron deposition in the liver. This was considered to provide evidence for the destruction of fetal red cells by some unknown toxic factor.

The main conclusions of the study were that more fetuses died as the result of excessive trauma during delivery than from maternal or fetal disease, that the fatal results of trauma were due to haemorrhage, and that maternal disorders may predispose to fetal injury during delivery.

This paper reminds us of the dramatic improvement in perinatal survival that has occurred over the past 60 years. The appalling mortality due to perinatal asphyxia and birth trauma recorded by Dr Tingle is unsurprising given the poor nutritional background of the population at the time combined with lack of such vital adjuncts to modern obstetric and perinatal care as antibiotics, safe obstetric anaesthesia, routine availability of blood transfusion, and the skills of modern neonatology. The progressive and continuing fall in deaths from trauma and asphyxia has highlighted a series of less tractable problems that were obscured amidst the perinatal carnage of 60 years ago.

The problems of preterm birth were hardly recognised at the time when Dr Tingle wrote her paper and received little mention within it. The term 'premature' was applied indiscriminately to any infant of low birth weight, with resultant confusion between preterm and growth retarded infants. This may partly account for the association noted between prematurity and intracranial trauma.

Some currently important areas of perinatal disease do find mention in the text. Thus two 'premature' infants developed intraventricular haemorrhage. They differed from the majority of such infants recognised now in having severe clotting abnormality.

An infant with generalised oedema, from the description almost certainly a case of rhesus isoimmunisation (not elucidated until 1940), was correctly recognised as suffering from destruction of the fetal blood by some unknown 'toxic factor'. Although rhesus isoimmunisation is now largely prevented, the problems of fetal oedema and non-immunological hydrops have become an important area for pathological investigation.

The problems of congenital anomaly, discussed by Tingle only in relation to the heart and skeleton now assume major importance with development of methods of antenatal diagnosis, genetic counselling, and in a few cases intrauterine surgery. The infant described as having achondroplasia, most probably a case of thanatophoric dwarfism, represents a group of infants, the lethal short limbed chondrodystrophies, that require cooperation between pathologist and geneticist for diagnosis and will need continuing biochemical investigation to determine the underlying mechanisms. In the 1980s the patterns of perinatal death presenting to the pathologist change at an increasing rate. The cases now referred to a regional specialist include a high proportion of second trimester fetuses requiring delineation, confirmation, or exclusion of congenital anomalies or fetal disease to link with the range of investigative approaches available to the clinician. The area of genetic disease other than gross anomalies found no place in Dr Tingle's study but is now becoming a major concern to pathologists with availability of antenatal biochemical diagnosis for many enzyme defects and the development of DNA probes for disorders such as Duchenne dystrophy and cystic fibrosis. Investigation of the causes and mechanisms of perinatal death has become a far more exciting and hopeful field of study than it was 60 years ago.

(Clara Tingle (or Clara Cross as she became after marriage) graduated from, and proceeded to MD at, Sheffield University. Later she moved to south west England where she set up the Department of Pathology and worked as a Consultant Pathologist in Bath. She introduced exchange transfusion for rhesus incompatibility in that area. She died earlier this year in the Unit named after her at St Martin's Hospital in Bath. She was, we believe, the only contributor to the inaugural issue of the *Archives* to have seen the beginning of its Diamond Jubilee year.)

(Jonathan Wigglesworth is Professor of Perinatal Pathology at the Royal Postgraduate Medical School, Hammersmith Hospital, London, and is a member of the Editorial Committee.)

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EFFECT OF ENCEPHALITIS LETHARGICA ON THE INTELLIGENCE OF CHILDREN.

BY

SHEPHERD DAWSON, M.A., D.Sc.,

AND

J. C. M. CONN, M.A.

(From the Medical Department, the Royal Hospital for Sick Children, and the Psychology Department, Jordanhill Training College, Glasgow.)

I.—INTRODUCTION.

Disturbances of mentality are probably the commonest and most striking of the after-effects of encephalitis lethargica. Duncan(8) found . . . .

Commentary

R J ROBINSON

This article is of historical interest for two different reasons. Firstly, it deals with a disease that swept round the world in the years immediately after the first world war, leaving devastating neurological disability in many of the survivors, but that then disappeared, its cause remaining an enigma. Secondly, it is fascinating to see that the approach used by these authors to the question 'Does encephalitis affect intelligence' was then clearly a novel one, though to us in 1986 it seems obvious and natural. It involved the use of psychometric testing on patients and controls followed by statistical comparison. Both methods were sufficiently unfamiliar to need full explanation, and the clear manner in which this is given makes the paper a pleasure to read.

The authors

Dr Shepherd Dawson, the senior author, was head of the Psychology Department at Jordanhill Training College, Glasgow. His interests included pathological factors affecting children's intelligence and the application of statistical methods to such studies, on which he published a practical manual. This study, like much of his research, was carried out at the Royal Hospital for Sick Children, Yorkhill. He died in 1935, aged 54. He was a distinguished figure in academic psychology, and his obituaries confirm, as can be guessed from this paper, that he was ahead of his time in the scientific application both of psychological testing and of statistics. Dr Conn was presumably a member of Dr Dawson's department.

The study

Forty six children ('The number of cases is not so great . . . as could be wished'!) had a definite diagnosis of encephalitis lethargica. They were given the Binet tests of intelligence as translated by Sir Cyril Burt. The controls were 974 children without encephalitis who had been tested in the same hospital. The mean intelligence quotient of the cases (84·63) was significantly lower than that of the controls (90·53). Subgroups from the cases were further analysed to see what factors were associated with the lowered intelligence. Intelligence was significantly lower in those whose disease had lasted more than 12 months, and the children who had been retested after an interval had mostly failed to show the appropriate increase in mental age. There was no difference in mean intelligence according to the presence or absence of a Parkinsonian syndrome or of behaviour disturbance.

No details are given of the ages or clinical features of the cases or controls, as would probably be expected now. Today's *Archives* reader might be more struck by the apparently rather small effect of this severe illness on intelligence than by the fact that there was an effect.

Encephalitis lethargica

This disorder was first described by von Economo in

1917 and occurred in a pandemic lasting from about 1917 to 1928. More than a million cases may have occurred world wide, with perhaps half a million deaths. Though the diagnosis seems to have been regarded as straightforward, the clinical picture was evidently variable. The typical acute cases showed headache, disturbance of sleep rhythm (with an emphasis on somnolence by day), and ophthalmoplegias. A wide variety of other neurological disturbances, however, such as cranial nerve palsies, behaviour disturbance, or extrapyramidal disorders might occur in the acute stage. Sometimes the onset was more gradual. Epidemics occurred in waves, with greater numbers in the winter months.

This account is based on what I have read[1] because there can be few living physicians with personal experience of the disease. The older of us, however, well remember seeing cases of postencephalitic Parkinsonism, and this late complication probably occurred in most survivors, greatly adding to the burden of disability caused by the pandemic.

Encephalitis lethargica was generally assumed to be caused by a specific virus, but no definite infective agent was ever identified. Some link with the influenza pandemic of 1918–19 was often suggested but not generally accepted because there was no close time relation between influenza and encephalitis, and because the encephalitis pandemic seems to have started before that of influenza. A relation between the two disorders, however, has recently been argued again,[2] and the newer understanding of slow virus infections, and of the long delay between acute measles infection and subacute sclerosing panencephalitis, makes a long latency between influenza and encephalitis more easily understandable. The exact cause remains a mystery.

Childhood encephalitis today

Though encephalitis lethargica no longer occurs, we still see children in whom a clinical diagnosis of encephalitis is made. They present with some combination of fever, fits, and depression of conscious level, their electroencephalogram is usually slow, and the cerebrospinal fluid may or may not show an excess of lymphocytes. In most cases the diagnosis remains a presumptive one, the main exceptions being herpes simplex encephalitis and encephalitis after an acute childhood infectious disease such as measles. In fact, a determined search for evidence of viral infection will reveal this in most cases.[3] The viruses concerned, which include entero- and adenoviruses as well as those already mentioned, are common, whereas encephalitis is rare, suggesting an abnormality of host response. The mechanisms producing encephalitis are becoming clearer, some forms such as herpes being the result of direct viral invasion or replication in the brain, whereas others such as measles are due to an abnormal immune response. The major recent advances in treatment have been the use of antiviral agents, particularly acyclovir for herpetic encephalitis, and closer neurological monitoring, with control of intracranial pressure in severe cases.

Many children make a complete recovery after viral encephalitis, though the prognosis is less good when the agent is measles and much worse if it is herpes. Even after other encephalitides an appreciable morbidity occurs, and studies like that done by Dawson and Conn 60 years ago remain important and relevant. The editors would still be delighted to receive a paper as clearly written as this one.

I am grateful to Dr and Mrs R R Gordon of Sheffield for the biographical information about Dr Dawson, who was Mrs Gordon's father. Dr Gordon is a member of the British Paediatric Association.

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(Roger Robinson is Professor of Paediatrics at the United Medical and Dental Schools of Guy's and St Thomas's, London. He was Editor of the Archives from 1969 to 1982; further details are given on page 984.)

Archives of Disease in Childhood, 1986, **61,** 966–968

ARCHIVES OF
DISEASE IN CHILDHOOD.

VOLUME I, 1926.

For wrapping the fish and chips?

S P LOCK

Several of the shafts in Richard Asher's 'Why are medical journals so dull?' were aimed at the *BMJ* (as he told me when I was his houseman).[1] Some, however, would have been just as appropriate to other targets; would these have included the first volume of the *Archives?* Certainly some of the externals are the very features that Asher stigmatised: drab cover, poor quality paper, unattractive titles, and overlong articles. Other contributors deal with the scientific quality of these; here I shall consider one aspect that Asher didn't touch on—the subediting—and one that he did—the style of writing.

Subediting

Another major enfant terrible of our time, Sir Peter Medawar, evoked a lot of applause when he called the scientific paper a fraud: science doesn't happen with the cosiness of the IMRAD structure (introduction, material and methods, results, and discussion), and so articles should be written to reflect reality.[2] This idea is fine when authors of Medawar's or Asher's calibre are writing, but most of the articles I have seen written in this fashion have all the likely clarity of Freud's first consultation with the Wolf Man. And it is impossible for the eavesreader to find out quickly at what pH the experiment was conducted or what the author thinks the message is (and not infrequently he leaves this out anyway). For most of us the IMRAD structure is a useful prop, particularly when each section of the article does no more and no less than is demanded of it, and Bradford Hill's series of questions is still the best guide for the tyro: 'Why did you start, what did you do, what answer did you get, and what does it mean anyway? That is a logical answer for a scientific paper.'[3]

The need for formality is well illustrated by volume 1 of the *Archives.* Some articles have summaries; others do not; others do not have subheadings at all, while any thought that there might be some consistent hierarchy or meaning to the sequence, size, or position of these where they are provided is soon dashed by finding that one article uses capitals, another italics, yet another both, and in either a central or shoulder position, or both. (The only regular feature is the old fashioned full point at the end of the title of the article, a subheading, or a table.) Finally, faced with the references, the obsessional gives up, blessing for once the Vancouver convention: what we now know universally as *JAMA* has no fewer than six different abbreviations,* two versions being seen in a single short reference list.

All this suggests, I believe, that if the articles were altered at all this was done by the printers, who would routinely have 'marked them up' for the press (a supposition confirmed by comparing the amateurish charts—presumably drawn by the authors—with the clear photomicrographs, some of them in passable colour). Illegally, the bound volume does not contain the names of the printers—but could they have been the BMA's own, dealing mainly with the *BMJ*, whose flat bed machines occupied the whole of the fourth floor of BMA House until 1935?†

The two editors had a small editorial board. Their prestigious names were no doubt there to give the journal a cachet; certainly, none of them is likely to have been concerned with subeditorship, although the occasional obsessional, such as the great Robert Muir, editor of *J Path Bact,* stands out by an insistence on meticulous preparation of manuscripts, often done around his own dining table.

The *Archives* board is also unlikely to have been concerned with peer review, let alone mundane matters; though review goes back to the beginning of serious scientific publishing, it was not all that widely practised in the 1920s, coming into routine use some 20 years later.[4] (Even in the 1960s the editor of *Nature* was said to choose most articles for publication by assessment within the office, taking the occasional difficult manuscript with him when he lunched at the Athenaeum in the hope that he would meet a colleague who could give him an expert opinion on it. (Maddox. Personal communication.))

Style

That the board took little active part in preparing the manuscripts is confirmed by the frequently printed 'pudder' or 'gobbledegook': to take only one member, the editor of the *BMJ*, in 1926 this was the renowned Sir Dawson Williams, a friend of the Fowlers and the Onionses, who was as likely to have put up with oxymoron or tautology as he was with the printers upstairs who settled their differences by fisticuffs (he sacked them). But, without tactful editorial help, Asher says, '[doctors] clog their meaning with muddy words and pompous prolixity; they spend little time in seeking the shortest, neatest, and plainest way of putting their meaning.' So in the *Archives* titles we have the redundant 'An investigation of . . .', 'Remarks on . . .', or 'Observations on . . .'. Any idea that before the antibiotic era there was a golden age of medical prose is dashed here by the frequent floating participles; the 'enlarged in size,' 'increased in number,' and 'aerogenous in nature'; and the sheer wordiness, seen typically, say, in Norman Capon's article on nephritis in childhood.

To say all this is not to sneer at the first volume of the *Archives*, a journal I have always skimmed for interest and pleasure. Journals when they start exist to serve the authorship rather than the readership; in fact, initially the two are the same, reflecting the invisible college that the journal was set up to serve, and a general readership that is not publishing much itself follows later. It is then that a good editor (of which the *Archives* has recently had several) must switch his priorities from his author to his reader, whose interests become paramount—and this means styling his manuscript in serviceable and intelligible prose, whatever the author's prima donnaish complaints.

In the 60 years since the *Archives* started we have lost something—true, not much, but something. Articles were not then overauthored or overreferenced: the mean number of authors per original article was 1·5 (range 1–4) in 1926, compared with 3·3 (range 1–12) in 1935; we were spared those awful declamatory titles that nowadays inhibit us from reading further ('Growth hormone inhibits atrial natriuretic factor production'); and editors were not pressured by authors bent on priority into what Stossel has called an 'arms race' of over-rapid publication or printing a whole history of the article (Received on . . .; suggested revision . . .; revised version received/accepted on . . .).[5]

The truth is that old journals interest a (very) few medical historians; most of us would prefer them out of the way, wrapping up the fish and chips. Whereas Asquith's policy over Irish Home Rule or Keynes's views on the Gold Standard can still be debated with valid interest, the reports of the 1930s on immuno-

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**Jnl Am Med Assn Chic; Jour Amer Med Assoc Chic; Jour Amer Med Assoc; Jnl Am Med Assoc Chicago; Jour Am Med Assn Chicago; J Am Med Assoc Chicago.* Concern over accurate references is not a mindless obsession: I would challenge anybody to retrieve some of those in this first volume, such is the paucity of information they give (no authors initials, or titles of the articles, for instance).

†One of the offices at the journal, the first I occupied, has a corner cupboard made out of the old lift shaft that carried the heavy lead type from the basement to the press.

transfusion or tuberculosis cannot. Much was produced around 1926 that has the same impact today: Stravinsky's *Oedipus Rex*, Aldous Huxley's *Point Counterpoint*, Henry Moore's first reclining figures. Better to revel in them and to celebrate the 60th anniversary of the *Archives* with the current issues, though in 2046 much the same will be said about these—and that is how it should be if medicine, and paediatrics, is to continue to advance.

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(Stephen Lock is editor of the *British Medical Journal* and has been a member of the editorial committee of the Archives since 1975.)

Sir Thomas Barlow, who wrote the introduction to the 1926 *Archives* (see pages 933–8 of this issue), was one of Jenner's assistants at University College Hospital, London, where he had qualified in 1871. Three years later he was a Registrar at The Hospital for Sick Children, Great Ormond Street, and within two years he was Assistant Physician at that Hospital and the Charing Cross Hospital. He occupied the Holme Chair of Clinical Medicine at University College Hospital from 1895 to 1907.

In 1883 he showed that infantile scurvy was identical with adult scurvy and that rickets was a separate disease, which became known as 'Barlow's disease'. He was Physician-Extraordinary to Queen Victoria, King Edward VII, and King George V. Barlow was President of the Royal College of Physicians during the controversy over the National Insurance Act. He had long been Senior Fellow on the College List when he died in his hundredth year.

Archives of Disease in Childhood, 1986, **61**, 969–971

Ancestors of the *Archives*

BERNARD VALMAN

In Europe and America specialist physicians, national societies, and journals devoted exclusively to the medical care of children were well established by the end of the last century. In Britain a few physicians would give an opinion on a sick child while retaining their interest in the medicine of the adult.

In 1896 an attempt was made to start an Anglo-American journal of children's diseases to be published simultaneously here and in America. The English edition of *Pediatrics* was not a financial success and was abandoned after a short time. The American publication grew rapidly despite the prestigious *Archives of Pediatrics* that had been published by the American Pediatric Society since 1884. The name of *Archives of Pediatrics* was changed to *Clinical Pediatrics* in 1926 and the last volume was published in 1930. Perhaps the change to a more modern and snappy title was a factor in the dissolution.

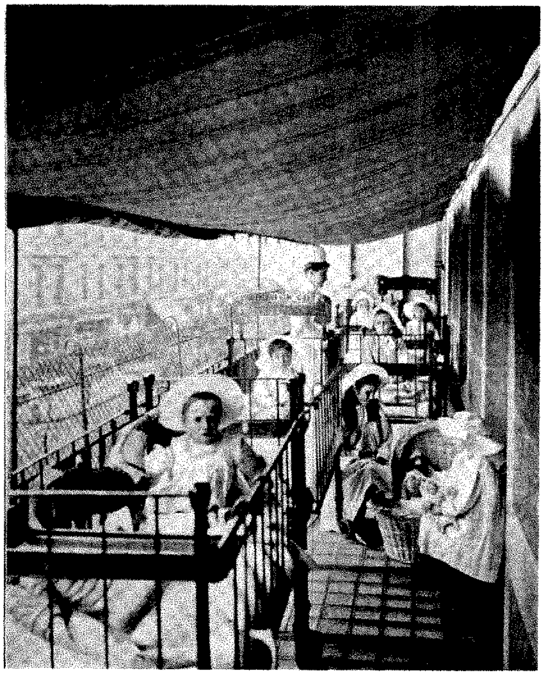
In England 'The Society for the Study of Disease in Children' was started in 1900. Clinical material for the meetings was largely supplied by physicians who worked mainly with children, but a large number of general practitioners attended the meetings, which were held in Brighton and Folkestone as well as Birmingham and London. Dr George Carpenter, who was Physician to the Evelina Hospital, London, edited an annual report for the Society, which was published by J and A Churchill. It was a substantial volume containing not only the results of papers on recent research but also clinical and pathological observations and the criticisms of the papers that had been heard at the meetings. Carpenter had probably been chosen as Editor because he had been appointed the English Editor of *Pediatrics* and had remained a member of the Editorial Board after the London edition ceased publication. These reports appeared annually until 1908 when the Society was incorporated into the Royal Society of Medicine.

Carpenter was elected Physician to the North Eastern Hospital for Sick Children, which later became The Queen Elizabeth Hospital for Children in Hackney Road, London (1903). At the same time he held the post of Medical Officer of Health for Beckenham. This was probably the reason for his special interest in the social aspects of children. About this time he saved the life of a child of R E Adlard, a printer, who agreed to finance and print a new paediatric journal with Carpenter as the Editor.

George Carpenter, MD

The British Journal of Children's Diseases first appeared in 1904. In the first editorial Carpenter wrote 'The object of the Journal will be to keep its readers in touch with the advances in knowledge in all that relates to the study of disease in children, whether of a scientific or practical nature. Its pages will not only be devoted to the study of disease in children, but to the prevention of disease, and to all that appertains to the welfare of children, whether physical or psychical. If *The Society for the Study of Disease in Children* and *The British Journal of Children's Diseases* can accomplish this good end, they will not only have justified their existence, but they will have accomplished a very worthy mission.'

The first paper was a case of hemicrania with third nerve paralysis by James Taylor, who was Physician to The National Hospital, Queen's Square. The second was a note on the antiquity of achondroplasia by George Pernet, who was Assistant to the Skin Department at University College Hospital, and described small glazed earthenware figures from Egyptian tombs showing the characteristic features. There was an article by Mr Clifford, Surgeon to St George's Hospital and the Belgrave Hospital for Children, on congenital hypertrophic stenosis of the pylorus in which pyloroplasty was performed. The next day the infant fed well but then developed gastroenteritis, a feature that was to be described at regular intervals in the pages of the Journal for the next 30 years. Mr Harold Burroughs described a case of Henoch's purpura in which a laparotomy was performed, and an accompanying editorial was on the aetiology of the visceral crises in Henoch's purpura. There was an editorial on the Employment of Children's Act and abstracts from the current literature, including a new treatment for whooping cough and the vitality of children of tabetics. In the signed book review section an author is rebuked for giving general practitioners confusing advice. The author had listed the treatment for a restless case of pneumonia as the following: 'Two leeches; a small blister; equal parts of chloroform belladonna and aconite liniments applied on lint; the ice bag; and cold lotions. The warm applications will generally be found to be the best. One, two, or three drops of nepenthe, one to three grains of Dover's powder or a small hypodermic injection of morphia'.



Open air treatment at the North Eastern Hospital for Children: medical balcony (below, left) and surgical balcony (above).

Carpenter wrote most of the editorials in a sparkling style covering many important aspects of the prevention and practical management of disease. He tackled the care of infants in workhouses, the high infant mortality and the new treatment of infectious diseases by exposure to fresh air (Figures). He presented and wrote up a large proportion of the patients presented at clinical meetings. He wrote three books; 'Congenital Affections of the Heart', 'Congenital Syphillis in Children in Everyday Practice', and 'Golden Rules for Diseases of Children'. Within a year he had formed an Editorial Board with six members elected from different parts of the country and two members from abroad. In March 1910 at the age of 50 years he died from a sudden cerebral haemorrhage.

Dr John Davey Rolleston, younger brother of the physician Sir Humphrey, became the next Editor and remained in that post for the next 34 years. He was Superintendent of the Western Fever Hospital in London and author of the standard textbook on acute infectious diseases. Although he had immense experience of the care of sick children, he was never recognised as a children's specialist. He continued Carpenter's policy of emphasising the social and practical aspects of the medical care of children as well as the description of physical disease. The number of pages printed gradually diminished to about 300 each year in the 1920s from 600 in Carpenter's day. The last volume in 1944 had only 66 pages. There was an original article on meningitis in children refractory to sulphonamides and a paper on the pathogenesis and clinical symptoms of tuberculous meningitis. In the final edition there were abstracts of a *1939* meeting (held five years previously) of the Royal Society of Medicine where there were presentations of kernicterus by Dr R S Illingworth, diabetes insipidus by Dr Donald Court, and subdural haematoma by Mr D W C Northfield. The Editor must have been desperate for material at this time because he then published an account of a meeting held 11 years earlier in *1933* at the Societié de Pédiatrie of Paris, a Society whose meetings Carpenter had attended regularly and reported promptly.

Photograph of the family of the case of hypertelorism reported in the 1926 Archives *volume 1.*

Archives of Disease in Childhood, 1986, **61**, 972–974

Archives of Disease in Childhood and the British Paediatric Association

This account of the founding and early years of the Journal by Alan Moncrieff was first published in 'The British Paediatric Association 1928–1952' by H C Cameron.

The *Archives of Disease in Childhood* first appeared in 1926, and was published by the British Medical Association, being the forerunner of many special journals. The question of the British Medical Association's undertaking responsibility for publication of subsidiary journals devoted to special subjects (on the lines of the policy followed by the American Medical Association) had been under discussion in B.M.A. committees in 1925. According to an article in the *British Medical Journal* (1926: 1. 209), "some of the medical men whose work lies chiefly among children" had suggested the publication of a new journal and an approach had been made to the British Medical Association. Doubtless Sir Dawson Williams, then Editor of the *British Medical Journal*, gave his support, for he had been a paediatrician before becoming a full-time medical journalist. However, it is recorded that difficulties were encountered which "suddenly" and "unexpectedly" dissolved and at a Council Meeting in July 1925, the British Medical Association agreed to publish the new journal (referred to as a "Journal of Paediatrics"). It is not possible, unfortunately, at this stage, to be certain who were the "medical men" referred to above. The article mentioned says they had been meeting together. Sir Robert Hutchison remembers nothing about any such meetings and Donald Paterson has no clear idea of the events leading up to the launching of the *Archives* except that the only other Paediatric journal *The British Journal of Children's Diseases* was getting worse! Presumably Hugh Thursfield and Reginald Miller must have had a lot to do with the affair, as they became the first editors. The first meeting of the editorial committee of the *Archives* took place in October 1925, with Dr. G. F. Still in the Chair. Others present were Thursfield, Cameron, Dingwall-Fordyce, Mr. H. A. T. Fairbank, Mr. Max Page and the editor of the *British Medical Journal*. Objections were raised to the use of "pediatrics" (American style!) in the title and after discussion the present one was adopted. According to the records Thursfield and Cameron had been the first choice as editors but Cameron was unable to accept and Reginald Miller was chosen. All this, of course, was going on before the British Paediatric Association had come into being.

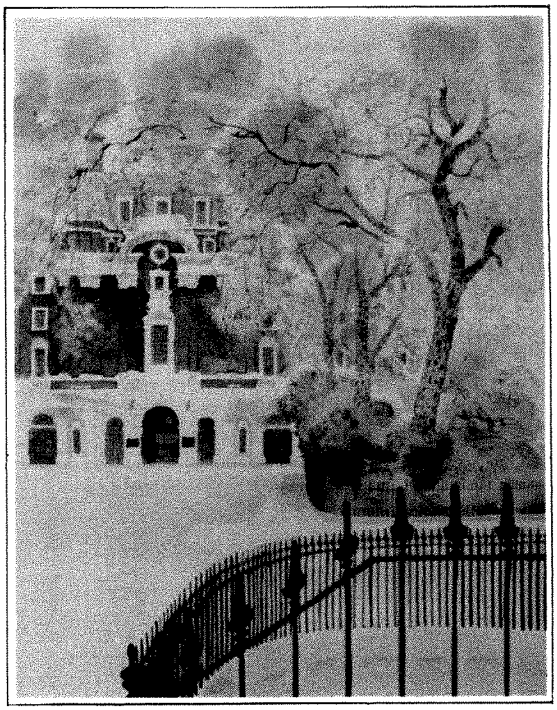
It follows, therefore, that although the British Paediatric Association used the *Archives* to publish the proceedings of its Annual General Meeting from the outset, the first such report appearing in 1928 in the third volume, and later, during the years of the second World War to publish reports on various subjects, there was at this stage no official connexion between the Association and the journal. From time to time, the question of a special journal owned by the Association was discussed unofficially, there being a school of thought which held that a substantial income for the Association might thereby be obtained! Matters came to a head in September 1943, when the Executive Committee had before it a letter from a firm of printers, Messrs. Adlard and Son Ltd. offering to transfer all rights in the *British Journal of Children's Diseases* to the British Paediatric Association. After considerable discussion it was decided not to accept this offer. In the course of the debate the question of an approach to the British Medical Association arose, and Alan Moncrieff, then one of the joint editors of the *Archives* was authorised to interview Dr. Hugh Clegg, deputy editor of the *British Medical Journal* on the question of the relations between the British Medical Association and the British Paediatric Association in reference to the *Archives*. Moncrieff reported to the next Executive Committee meeting that it looked as if the British Medical Association might consider recognition of the *Archives* as the official journal of the British Paediatric Association and accordingly the then President, Leonard Parsons, sent a letter to the Journal Committee of the British Medical Association asking that this should be effected. The Journal Committee apparently discussed the matter and then asked Moncrieff to come for further discussions with the Chairman of the Council of the British Medical Association, the acting Secretary, Dr. Charles Hill, the Chairman of the Journal Committee, the Editor of the *British Medical Journal* and the Deputy Editor, Dr. Hugh Clegg. The result of this was a rejection of the idea of making the *Archives* the official organ of the British Paediatric Association, together with an

British Paediatric Association, 5 St Andrews Place, Regent's Park, London.

offer to allow the appointment of editors, editorial committee and the general advisory board to be made by the British Paediatric Association, this fact to be noted on the cover and elsewhere. Another suggestion was that the appointments should be made jointly by the two Associations and this fact be suitably noted in appropriate places.

All this was reported by Moncrieff to an Executive Committee in November 1943, and eventually confirmed by a letter from Dr. Clegg to Parsons at the end of the year. At the first Executive Committee meeting in January 1944, Dr. Hugh Clegg and Dr. Charles Hill attended for further discussion. General matters concerning the relationship between the two Associations were debated but the subject is not relevant here. Regarding the *Archives* the second of the two foregoing alternatives was accepted. The British Paediatric Association was to nominate the editors, the editorial committee and the general advisory board, these nominations being subject to the approval of the British Medical Association, so that in effect the appointments were initiated by the British Paediatric Association and ratified by the British Medical Association. It was agreed that members of the editorial committee should serve for three years and that the President of the British Paediatric Association and the Editor of the *British Medical Journal* should be *ex-officio* members of this committee. The possibilities of a part-time payment to an editor was discussed. (Later the British Medical Association supplied the sub-editorial assistance for all its special journals as required.)

All this appears to have taken a surprising amount of time, meetings and correspondence. Parsons, Moncrieff and A. W. Franklin were appointed to serve on a joint committee with members of the Journal Committee of the British Medical Association, partly to discuss further the matters mentioned above, but also because the *British Journal of Children's Disease* had now come into the story again. Dr. Clegg had approached Messrs. Adlard and Son Ltd. in December 1943, about the future of their journal. Eventually the Journal Committee



Archives *Editorial Office in British Medical Association House, Tavistock Square, London.*

and the Council of the British Medical Association agreed to purchase the rights of the *British Journal of Children's Diseases* "without prejudice to future publication and without conditions as to the printing thereof". This was duly reported to an Executive Committee in September 1944. The editorial committee of the *Archives* now duly nominated by the British Paediatric Association then met, and it was decided to add to the title of *Archives of Disease in Childhood* the words "incorporating the British Journal of Children's Diseases". The new wording regarding the appointment of editors and editorial committee was also approved and for the first issue of the next year, March 1945, the words "British Paediatric Association" appeared on the cover of the *Archives* for the first time. To this may be added a phrase in a letter from Dr. Clegg to Parsons regarding this point, namely that the name on the cover would "make it quite clear to the medical world generally that editorial policy and editorial direction are provided by your Association".

The Honorary Secretary, reporting these facts to the Annual General Meeting in 1945 stated that "your Association is officially associated for the first time with the management of this Journal".

No great change in the arrangements has since been made. The machinery for nomination and so forth worked smoothly when set in motion. If changes on the cover during the current year were to be avoided, however, someone had to remember in good time that nominations had to be made some six to nine months before the next year's volume appeared. Also, the period of three years was found in practice to be too short a time for membership of the Editorial Committee.

In 1954, with the agreement of all concerned, the annual meeting of the Editorial Committee, which used to be held in the summer, was changed to a time when its recommendations could go to the impending February meeting of the B.P.A. Executive Committee. Thence, after approval by the Annual Meeting of the B.P.A. the nominations are sent to the B.M.A. for their consideration, so that editorial changes are made in good time for the first number of the *Archives* for the ensuing year. In 1954 also, membership of the Editorial Committee was extended to five years.

Dr Douglas Gairdner, editor 1964–79, writes:

A possibly interesting commentary on the way things like appointing an editor used to go in the days when the BPA was smaller, more casual, and less professional is my recollection of a Council meeting in, I think, 1953. At the end of a long agenda came one more item—'Resignation of Dr Philip Evans from Editorship of *Archives*'. The Chairman asked for suggestions for a replacement. None were immediately forthcoming, and there was quite a long silence. I looked round the table and saw Richard Dobbs, and mentioned his name as a possibility. He looked a little startled, but there was little hesitation from the others before he was unanimously appointed. Later, Ian Cathie expressed wry surprise that his co-Editor should have been appointed without any consultation with him (in fact, the two worked very harmoniously from 1954–1963). When Ian Cathie retired in 1963, Richard Dobbs invited me to join him, and this was endorsed by Council—a pattern that I presume has been maintained subsequently.

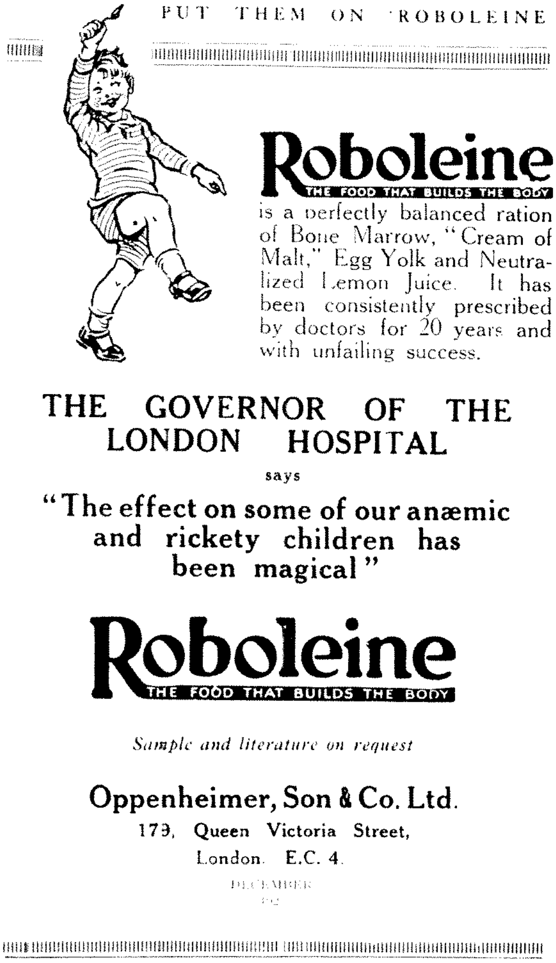
Archives of Disease in Childhood, 1986, **61,** 975–978

Archives 1926–86

In the early years of the journal there were long descriptions of disease with extensive details of postmortem examination, including histology. The prevalence of common diseases in specific parts of cities was documented carefully. There was very little about the newborn. Papers were often 20 pages in length and contained tedious detail in small print that few modern readers would tolerate. In recent years we have published an increasing number of papers on the newborn, especially the preterm infant, biochemistry, molecular biology, scanning by ultrasound, computerised axial tomography, and nuclear magnetic resonance. Advertisements are based on the results of clinical trials rather than opinions (Figure).

At first the journal was published quarterly and between 1951 and 1973 it appeared every two months. The short reports section was introduced in 1970, and monthly publication began in 1973. There was a Technical Editor to run the journal on a day to

"Then . . . .



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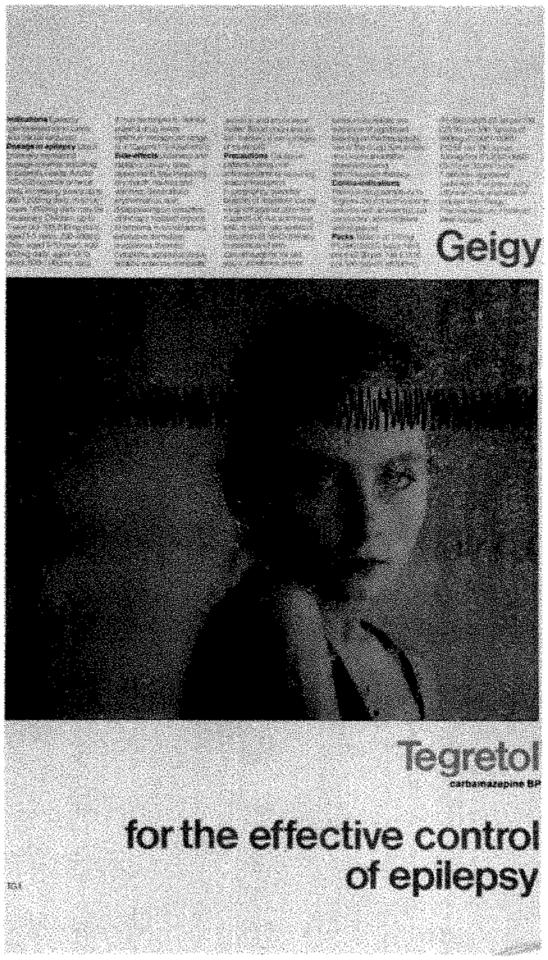

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day basis, prepare material for printers, and check proofs before 1952. The names of Technical Editors did not appear inside the cover until 1973. There have always been two Editors of the journal, and apart from the pathologist Ian Cathie they have been full time paediatricians who have carried out their editorial work in their spare time.

The journal was founded and owned initially by the British Medical Association. Dr Stephen Lock, Editor of the *British Medical Journal*, negotiated a new agreement on behalf of the British Medical Association in 1977. The British Medical Association and the British Paediatric Association became equal partners sharing the profits or losses of the journal with up to 800 free copies being supplied to the British Paediatric Association. The agreement was slightly altered in 1981 as a consequence of the considerable growth in the membership of the British Paediatric Association and a new scheme of sharing costs and profits between the two associations was introduced, on the basis of other successful agreements between the British Medical Association and the societies co-owning journals. A group of referees who make a particularly large contribution to the journal form the Editorial Committee, which meets once a year and helps to determine policy. An Associate Editor for perinatal medicine was appointed in 1985. Financial aspects of the journal are the responsibility of the Management Committee, which is composed of the two Editors, two other representatives of the British Paediatric Association, and four representatives of the British Medical Association.

Over the past five years the number of pages has increased from about 1000 to 1250. In 1973 there were two annotations a year, and in 1985 there were 24 annotations with nine personal practice papers and 10 current topic articles. We receive over 800 original articles and over 1000 new manuscripts each year. Original articles are published about five months and short reports about three months after the receipt of an acceptable manuscript. The number of subscribers has remained constant over the past five years, although most of the specialist journals are experiencing a loss of 5% of subscribers each year. About three fifths of our subscribers are outside the United Kingdom.

The following papers have been selected and summarised from the *Archives* to show the variety of authors, changing medical practice, or the first or best description of a new finding.

1928
Anaemia in infancy due to iron deficiency has a high prevalence.
MacKay H M M.

1933
First description of Kwashiorkor.
Williams C.

1939
Early reports of the effects of sulphonamides.
Gaisford W F, Morris N, Moncrieff A, and Fleming G B.

The high incidence of spasticity or other cerebral defects in infants who were born prematurely.
Illingworth R S.

1943
Observations on infant behaviour.
Winnicott D W.

1948
Fibrocystic disease reported in siblings and appeared to have high familial incidence.
MacGregor A R.

1950
Rubella seems able to attack optic lens and cardiovascular system during embryogenesis.
St Huggett A.

1952
Retrolental fibroplasia found in 56 babies in a special care unit during the years 1947–51, suspicion falling on the adverse effect of sudden fluctuations of available oxygen.
Jefferson E.

1954
Haemolytic disease of the newborn had occurred in 27 out of 891 children with congenital perceptive deafness, selective high tone deafness being the main defect.
Fisch L and Osborne D A.

1955
Galactosaemia is recorded for the first time trans-

mitted as a homozygous recessive gene in the offspring of a consanguineous marriage.
Holzel A and Komrower G M.

1961
First five years of life are critical for diagnosis, treatment, and training of children with speech defects.
Sheridan M D.

1963
Homocystinuria: a new inborn error of metabolism.
Carson N A J, Cusworth D C, Dent C E, Field C M B, Neill D W, and Westall R G.

1966
First comprehensive British growth charts, which were subsequently used throughout the world for growth and development records.
Tanner J M, Whitehouse R H, and Takaishi M.

1967
Sugar malabsorption due to deficiencies of disaccharidase activities and of monosaccharide transport.
Holzel A.

First description of methylmalonic aciduria causing metabolic acidosis.
Oberholzer V G, Levin B, Burgess E A, and Young W F.

1970
A thermal neutral environment reduces oxygen consumption and evaporative water loss to a minimum.
Hey E M and Katz G.

1971
Effect of human growth hormone treatment for 1–7 years on growth of a hundred children.
Tanner J M, Whitehouse R H, Hughes P C R, and Vince F P.

1972
Renal transplantation in 19 children.
Hulme B, Kenyon J R, Owen K, Snell M, Mowbray J F, Porter K A, Starkie S J, Muras H, and Peart W S.

1973
Criteria for identifying children who may be at increased risk of unexpected death.
Protestos C D, Carpenter R G, McWeeny P M, and Emery J L.

Changes in ventilator management reduced mortality from hyaline membrane disease and incidence of bronchopulmonary dysplasia.
Herman S and Reynolds E O R.

1974
Good correlation between arterial and transcutaneous oxygen levels in the newborn.
Huch R, Lubbers D W, and Huch A.

1975
Urinary tract in schoolgirls with covert bacteriuria.
McLachlan M S F, Meller S T, Verrier Jones E R, Asscher A W, Fletcher E W L, Mayon-White R T, Ledingham J G G, Smith J C, and Johnston H H.

1976
Fifteen year developmental study on the effects of severe undernutrition during infancy on subsequent physical growth and intellectual functioning.
Stoch M B and Smythe P M.

Diabetic ketosis treated by adding low dose insulin to rehydrating fluid.
Malleson P N.

1977
Increasing breast feeding in the community.
Sloper K S, Elsden E, and Baum J D.

1978
Computed axial tomography and acute neurological problems of childhood.
Day R E, Thompson J L G, and Schutt W H.

Viral infection as a precipitant of wheeze in children; combined home and hospital study.
Mitchell I, Inglish J M, and Simpson H.

1979
A clinical comparison of beclomethasone dipropionate delivered by pressurised aerosol and as a powder from a rotahaler.
Edmunds A T, McKenzie S, Tooley M, and Godfrey S.

1980
Development of gut hormone responses to feeding in neonates.
Lucas A, Bloom S R, and Aynsley-Green A.

Continuous sodium valproate or phenobarbitone in the prevention of simple febrile convulsions. Comparison by a double blind trial.
Ngwane E and Bower B.

1981
Cerebral structure and intraventricular haemor-

rhage in the neonate; a real time ultrasound study.
Levene M I, Wigglesworth J S, and Dubowitz V.

Hyperphenylalaninaemia in the quarter of a million neonates tested in a screening programme.
Walker V, Clayton B E, Ersser R S, Francis D E M, Lilly P, Seakins J W T, Smith I, and Whiteman PD.

1982
Munchausen syndrome by proxy.
Meadow S R.

1983
Nuclear magnetic resonance imaging of the brain.
Bydder G M and Whitelaw A.

1984
Clinical use of DNA markers linked to the gene for Duchenne muscular dystrophy.
Pembrey M E, Davies K E, Winter R M, Elles R G, Williamson R, Fazzone T A, and Walker C.

1985
Virulence genes in prevention of *Haemophilus influenzae* infections.
Moxon E R.

BV

Dr Philip Evans, editor 1948–54, writes:

The first article in the *Archives* was on cirrhosis of the liver in childhood by F J Poynton and W G Wyllie.* In it three cases in one family were described, two sisters and a brother. The same patients appeared in about 1935 in an article in *The Quarterly Journal of Medicine*, this time on glycogen storage disease (was Von Gierke's paper 1929?). The worst affected of the sisters turned up at Guy's Hospital to have her first and probably only baby in about 1950. She was a short stumpy figure with a huge hard liver, cheery and full of energy, which she attributed to physical training at school. The baby boy was unaffected. She was followed up by Edward W Holling who eventually published a paper about her.

*The article is reviewed by A P Mowat on page 941.

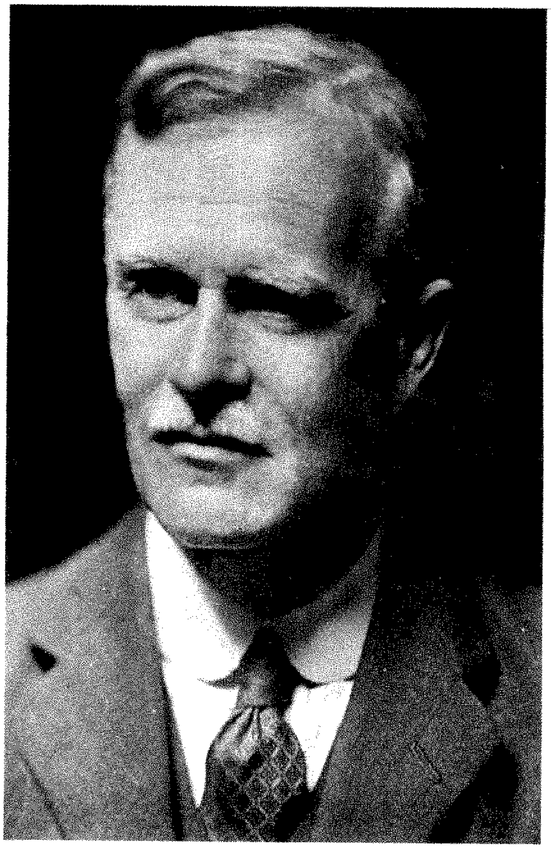
Archives of Disease in Childhood, 1986, **61**, 979–984

Editors of the *Archives*

Hugh Thursfield and Reginald Miller	1926–33
Charles Harris and Alan Moncrieff	1934–38
Alan Moncrieff and Richard Ellis	1939–45
Richard Ellis	1946–47
Richard Ellis and Philip Evans	1948–49
Philip Evans and Ian Cathie	1950–54
Ian Cathie and Richard Dobbs	1954–63
Richard Dobbs and Douglas Gairdner	1964–69
Douglas Gairdner and Roger Robinson	1969–79
Roger Robinson and Roy Meadow	1979–82
Roy Meadow and Bernard Valman	1982–

Hugh Thursfield (1869–1944)

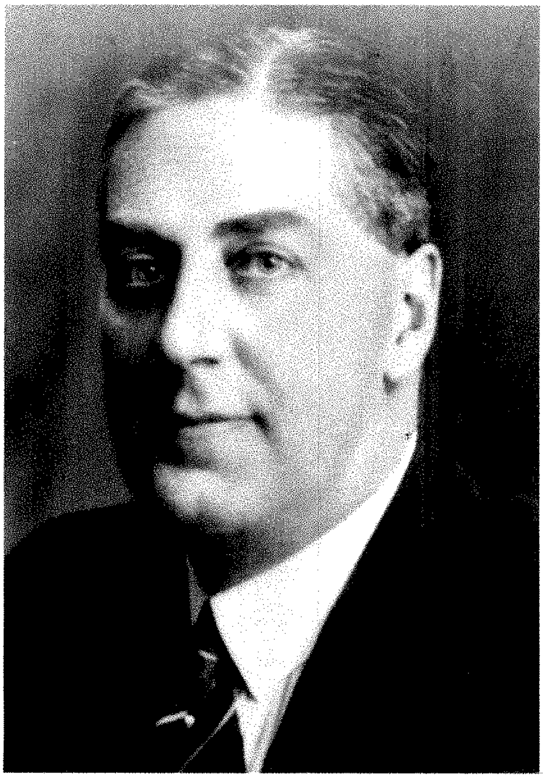
From Trinity College, Oxford, where he took a First in Mods he went to St Bartholomew's Hospital and became a member of the staff. He was demonstrator of Morbid Anatomy for many years and published a popular book 'Medical Morbid Anatomy and Pathology'. Promotion at Bart's was apt to be slow and he was still an Assistant Physician in charge of the Children's Department when he retired. All his life he was a student of the Classics. To him the Odyssey was the finest story in the world and one that a wise man should read most nights for a while before going to bed. He played a major part in the production of a great paediatric textbook by Garrod, Batten, and Thursfield. Anyone in search of information would find that he could generally supply the answer, whether it concerned the signs of the Zodiac or the dates of all the editions of the Encyclopaedia Britannica. A bachelor, he had a great knowledge of food and how to serve it, and he was a fine judge of claret.



Hugh Thursfield

Reginald Miller (1879–1948)

He was appointed as a General Physician to St Mary's Hospital, London, although most of his paediatric work was done at the Paddington Green Children's Hospital. He wrote articles on coeliac disease and various forms of vomiting, but his special interest was in rheumatic diseases of childhood and he was the first in this country to establish a supervisory clinic for rheumatic children. As a young man, too young perhaps, he published a text



Reginald Miller

book 'The Medical Diseases of Children'. The reviewers deplored the lack of personal observation and he took their criticism to heart and refused a request for a second edition. He attended very few meetings of the British Paediatric Association and at committee meetings he generally kept silent. When he did speak, his carefully chosen comments or criticisms could be devastating. He was a master of words who wrote little and a wit who preferred to be alone.

Sir Charles Harris (1900–1974)

He was born in New York, spent his childhood in Australia, and qualified at St Bartholomew's Hospital. After a period at John Hopkins Medical School, Baltimore, he was appointed Assistant Physician at Bart's in 1928. The department at that time was represented only in outpatients; children who were inpatients were cared for by the general physicians. After a struggle a separate children's department with its own ward was achieved within a year. In addition he was Physician to the Westminster Hospital for Children and Consultant Paediatrician to the London County Council. Harris was President of the British Paediatric Association in 1962.

He was a brilliant administrator and over 25 years ascended from Warden of the Medical College to Vice-Chancellor of London University. He held himself rather aloof and seemed to enjoy his ability to keep people guessing about his true beliefs. This could be carried to the extreme by opposing what he really wanted in the first round of a discussion.

Sir Charles Harris

Sir Alan Moncrieff (1901–1971)

After various posts at the Middlesex Hospital and the Hospital for Sick Children, Great Ormond Street, between 1922 and 1934 he was appointed to the staff of both hospitals. In 1924 he had worked in Paris in the Health Division of the League of Red Cross Societies and in 1930 he studied in Germany

Sir Alan Moncrieff

with a Rockefeller Travelling Fellowship. His special interest was respiratory failure, including asphyxia in the newborn. He was also Paediatrician to Queen Charlotte's Maternity Hospital and Hammersmith Hospital and a part time School Medical Officer to the London County Council.

He was author of 'Child Health and the State' in 1953, Editor and part author of 'Text Book on the Nursing and Diseases of Sick Children', and joint Editor of 'Diseases of Children'. He wrote a hand book for *The Practitioner* on child health and was medical correspondent to *The Times*.

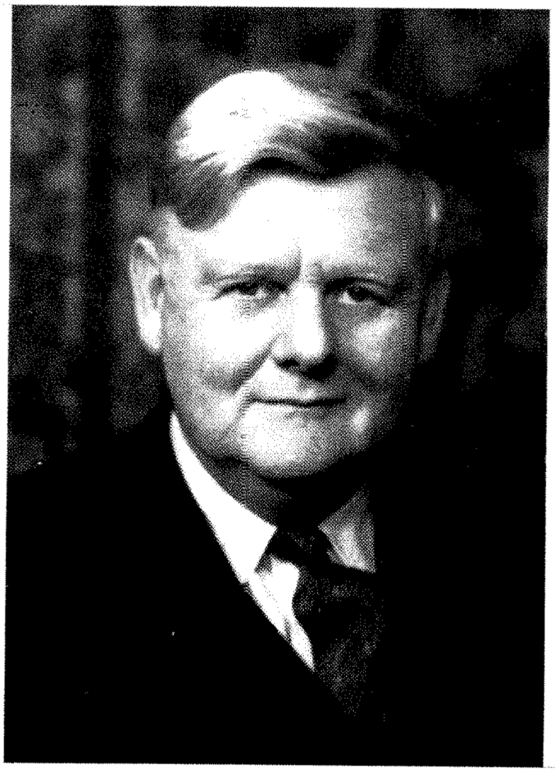
This would have been enough to occupy most men, but Moncrieff, with his capacity for concentration and genius for organising his working day, found time for many other activities. As a Justice of the Peace he worked in the Juvenile Courts in London and became chairman of many committees, including the Central Midwives' Board and the British Medical Association Journal Committee.

When the Institute of Child Health was founded at Great Ormond Street in 1946 Moncrieff was appointed to the first Nuffield Chair of Child Health. He incorporated an infant welfare centre as part of the Institute and established the Department of Growth and Development and the UNICEF Department of Tropical Medicine.

Moncrieff was the first holder of the James Spence Medal and was Honorary Secretary and later President of the British Paediatric Association.

Richard Ellis (1902–1966)

After two years at the Boston Children's Hospital where he was known as The English Doctor by his ruddy cheeked round face adorned with side whiskers he became Assistant Physician at Guy's with Hector Cameron. The Infant and Child Welfare Centre in the precincts of the hospital department introduced him to community child health. His spirit of service carried him with the Society of Friends to the Spanish Civil War where he arranged for the

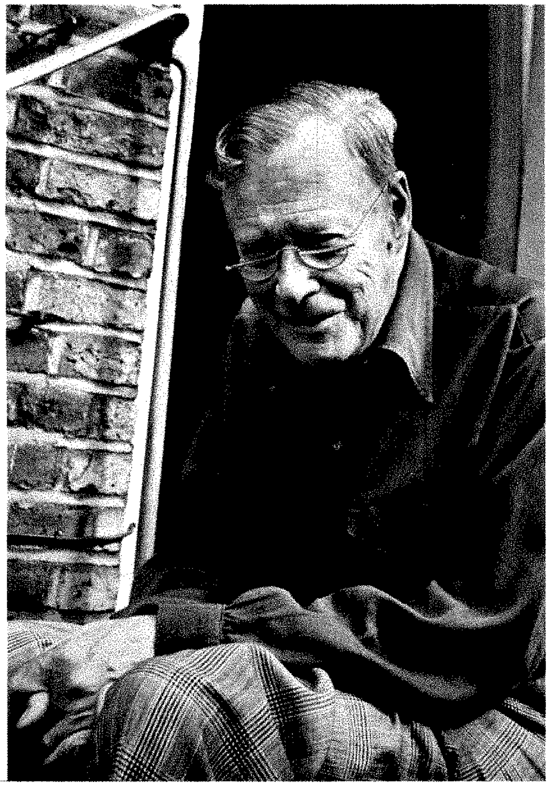


Richard Ellis

evacuation of 4000 Basque children to Britain. In 1939 he was in Romania and Hungary caring for Polish refugees. He earned distinctions in the second world war through his long service in the RAF but also managed to find time to edit the *Archives* and to study the incidence of vitamin deficiencies in children and the natural history of the skeletal changes in early rickets.

In 1946 he became Professor of Child Life and Health in Edinburgh and the following year published 'Child Health and Development', which expressed his views on trying to improve child health gradually, emphasising the social, economic, and cultural aspects. This broad interest in child health contrasts with his earlier attraction to the rare and obtruse.

In 'Diseases in Infancy and Childhood' and 'Health in Childhood' he showed the undergraduate and family doctor how to prevent and manage diseases and what statutory and voluntary social services existed. He was President of the BPA in 1965–66, but ill health prevented him from carrying out his duties.



Philip Evans

Philip Evans

After graduating at Manchester University he became a Rockefeller Research Fellow at the Presbyterian Hospital, New York. The following year he became Director of the outpatient clinics at John Hopkins Hospital. Between 1939 and 1946 he was Assistant Physician at King's College Hospital and was then appointed Director of the Department of Paediatrics at Guy's Hospital and Physician at the Hospital for Sick Children, Great Ormond Street. In addition to his busy clinical practice he was Honorary Secretary to the British Paediatric Association, Censor of the Royal College of Physicians, and Director of the British Tay Sachs Foundation. In 1967–68 he won the admiration of paediatricians throughout the world as Director of the first British medical team in Saigon, which was ravaged by war.

His first research interests were in rheumatic fever and later pink disease followed by cerebral palsy. In 1948, meditating on the shore of Lake Zurich, he decided to concentrate on congenital disorders but he maintained his interest in general paediatrics and his name came to mind first when a paediatrician sought help with his own sick child.

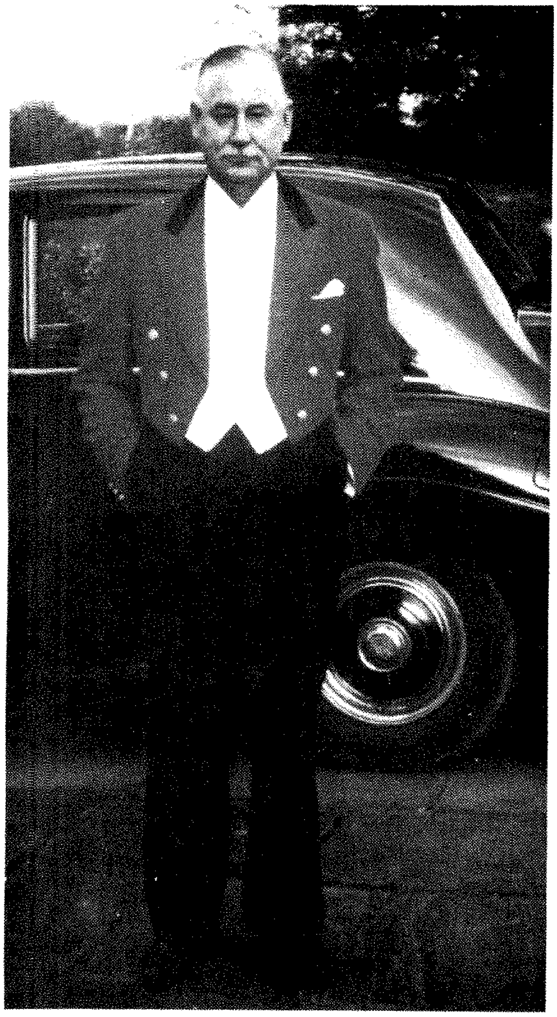
He published 'Infant Feeding and Feeding Difficulties' with RC MacKeith and was the Joint Editor of the 1953 edition of Garrod, Batten, and Thursfield's 'Diseases of Children'. By 1978 he had published more than 55 original articles and 130 reviews and invited articles, including a series of 'Letters from London' in the *American Journal of Diseases of Children*.

He lives in retirement in St John's Wood, London.

Ian Cathie

Ian Cathie qualified at Guy's Hospital in 1932 and four years later was appointed Pathologist to the Christie Hospital and Holt Radium Institute in Manchester. In 1938 he was appointed Clinical Pathologist at The Hospital for Sick Children, Great Ormond Street, and remained there until he retired in 1958. His research interests included penicillin, when the ration for the whole hospital was 1 gram per month, and later streptomycin. Between 1950 and 1960 his laboratory was an international centre for the serological diagnosis of toxoplasmosis. He also published papers on haematology, bacteriology, and fibrinolysin.

He retired to Moreton-in-Marsh where he has been trying to breed homozygous Hereford bulls.



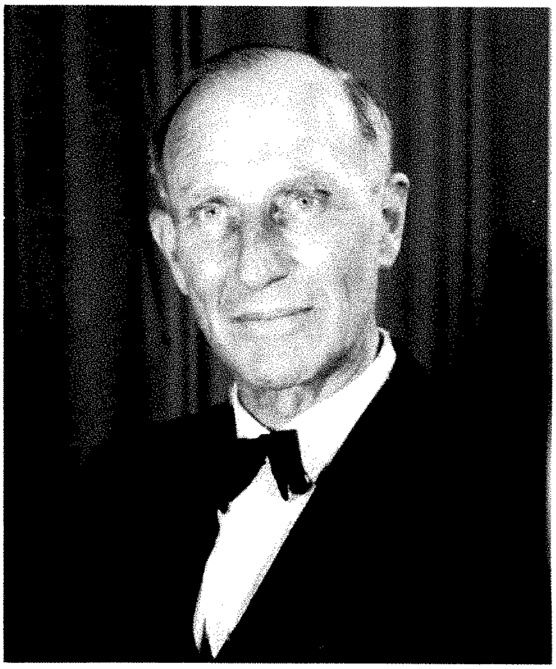
Ian Cathie

Richard Dobbs (1905–1980)

While a medical student at The London Hospital he persuaded the Dean to allow him to go for a year of his clinical course to Vienna, which was then living largely on its reputation obtained before the first world war. He spent some time at The Children's Hospital, St Louis, and was then appointed to the three hospitals in which he was to work for the next 30 years—The London Hospital, The Queen Elizabeth Hospital for Children, Hackney, and Southend General Hospital. He was President of the British Paediatric Association in 1970.

When a boy of 10 he had severe nephrotic syndrome and Sir Frederick Still was called in, who asked him what he intended to be when he grew up, and Richard replied 'I want to be a children's doctor like you, Sir'. Their next meeting occurred some 15 years later when Still examined him for the MRCP and was able to recall their earlier conversation.

In middle age he took up sailing and despite minimal experience sailed his 45 foot *Natasha* in ocean races. After his formal retirement he spent six months with the Grenfell Mission in Labrador before going to Nigeria as Professor of Paediatrics at Ahmadu Bello University, Zaria.



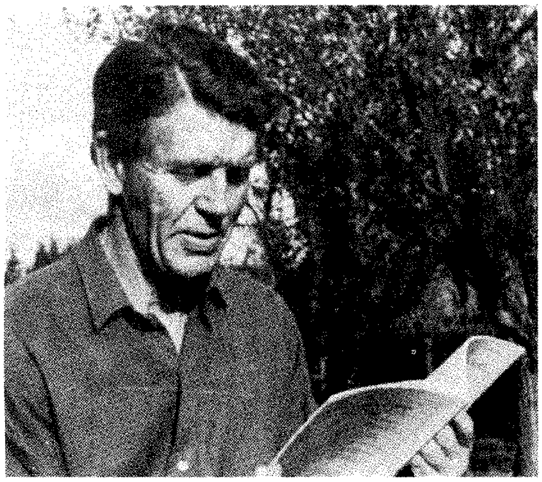
Richard Dobbs

Douglas Gairdner

Douglas Gairdner is still living in Cambridge where he worked as Consultant Paediatrician between 1948 and 1975. He went up to Oxford to read Chemistry but then changed to Medicine. After qualifying at the Middlesex Hospital and a two year post of Outpatient Registrar at Great Ormond Street he became a Fellow in Paediatrics at the Bellevue Hospital, New York, during 1939. During the war he served in the Royal Army Medical

Corps, mainly in the Middle East, and then became First Assistant to Professor James Spence in Newcastle for three years.

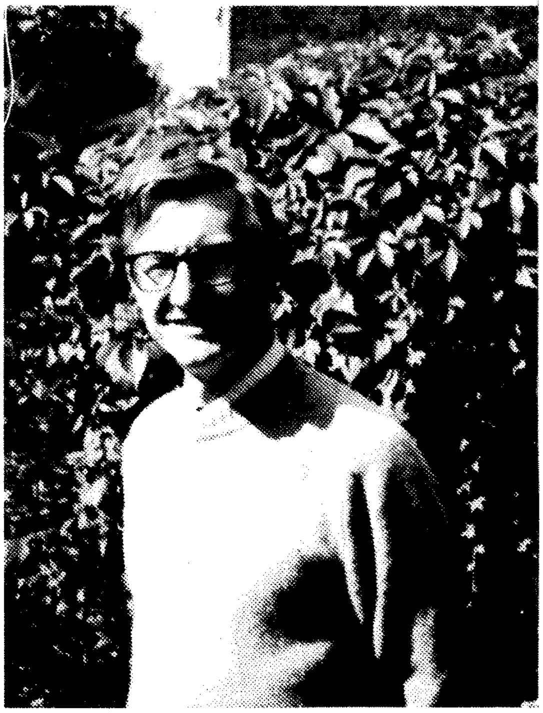
His Doctor of Medicine thesis was on Henoch-Schönlein syndrome and his other research interests have included the nephrotic syndrome, blood formation in infancy, the pathogenesis and management of hyaline membrane disease, and the natural history of adipose cell development in children. 'The Fate of the Foreskin' written with Spence's encouragement remains a model of perceptive and pungent writing on the frontier of fact and fashion. Gairdner was the James Spence Medallist in 1976. He was Editor of the first four editions of 'Recent Advances in Paediatrics' and he still maintains his twin interests in sailing and writing by editing the Cruising Association's bulletin.



Douglas Gairdner

Roger Robinson

After Balliol College and the Radcliffe Infirmary in Oxford, he went to Hammersmith Hospital. He became Research Fellow in Boston and visiting Lecturer in Kentucky. Robinson returned to become Senior Lecturer at Hammersmith Hospital and then Consultant Paediatrician and four years later the first Professor of Paediatrics at Guy's Hospital. He has kept a strong foot in general paediatrics as well as being a paediatric neurologist with special interests in language disorders, epilepsy, and the newborn. His earlier research was on carbohydrate metabolism and most of his later articles have been on neurology. He edited two books, 'Brain and Early Behaviour' and 'Congenital Malformations'. The general reader will remember him by his outstanding wisdom and clarity of thought in his leading articles in the *Archives* and *British Medical Journal*. 'The Whooping Cough Immunisation Controversy', 'Research Involving Children: Ethics, the Law and the Ȼlimate of Opinion', and 'The Child Who is Slow to Talk' are superb examples of the quality of his style.



Roger Robinson

BERNARD VALMAN

Archives of Disease in Childhood, 1986, **61,** 985

1926—A year to remember

The politburo expels Leon Trotsky and Grigori Zinoviev; Josef Stalin is established as dictator of the Soviet Union.

Chiang Kai Shek succeeds Sun Yan-Sen as leader of the Chinese Revolutionary Party.

Chancellor of the Exchequer Winston Churchill returns Britain to gold standard. Export industries such as coal come under severe pressure and private mine owners attempt to cut wages for miners; the general strike results.

United States troops land in Nicaragua 'to preserve order and to protect US interests'.

Adoption of children is legalised in England. A government Act allows legitimisation of children born out of wedlock providing parents subsequently marry.

New books

History of England by G M Trevelyan.
Dictionary of Modern English Usage by H W Fowler.
Seven Pillars of Wisdom by T E Lawrence.
Winnie the Pooh by A A Milne.
Archives of Disease in Childhood by Thursfield and Miller.
La Fin de Chéri by Collette.
Ideal Marriage by T H Van de Velde.

First performances

Symphony No 7 in C major, Sibelius.
Symphony No 1, Shostakovich.
The Desert Song, Romberg and Hammerstein.
The Plough and the Starts, Sean O'Casey.
The Constant Wife, Somerset Maughan.

First showings

Lover's Bouquet, Chagall.
Several Circles, Kadinsky.
Draped Reclining Figure, Henry Moore.

John L Baird successfully shows television using mechanical scanning disc.
R H Goddard launches the first liquid fuelled rocket from a field in Massachusetts. Although it reaches a height of only 41 feet, he is convinced that one day rockets will land men on the moon.
Charles Lindbergh flies the first scheduled mail flight, between St Louis and Chicago.
The Schneider Trophy air race is won by Italy with a speed of 256 mph.
The new model T Ford car with a self starter costs $350.
The first motion picture with sound is shown.

The Nobel Prize for Literature is presented to George Bernard Shaw.

A daughter (Elizabeth Alexandra Mary, later to be Queen Elizabeth II) is born to the Duchess of York on 21 April.

H D Lee Company in Kansas introduce blue jeans.
Slide fasteners are called zippers for the first time by novelist Gilbert Frankau: 'zip it's open, zip it's closed'.

Al Capone's Chicago headquarters are sprayed with machine gun fire during prohibition.
Flavoured yoghurt is produced in France.

Oral liver extract is introduced to treat pernicious anaemia.
Sunlight is shown to convert ergosterol into vitamin D.
Thyroxine is synthesised for the first time.

Oil is discovered in Iraq.

Gene Tunney wins World Heavyweight Boxing Championships from Jack Dempsey.

Harry Houdini remains under water for 91 minutes in an air tight case containing enough air for five minutes. He died three months later from peritonitis.

HAPPY BIRTHDAY ARCHIVES!
THE SAME TO YOU MA'AM
ARCHIVES OF DISEASE IN CHILDHOOD
e Journal of the British Paedi
Association
THE QUEEN AT 60

Archives of Disease in Childhood, 1986, **61,** 987–989

Our referees

Submitted manuscripts are initially seen by the Editors who then send them to one or two expert referees for their assessment. Last year the following people kindly reviewed papers for our Journal. We thank them and at the same time thank the many hundreds of referees who have assessed papers for us in the previous 60 years of our Journal's history. Their expertise and the time so generously given has been a major factor in maintaining high standards.

THE EDITORS

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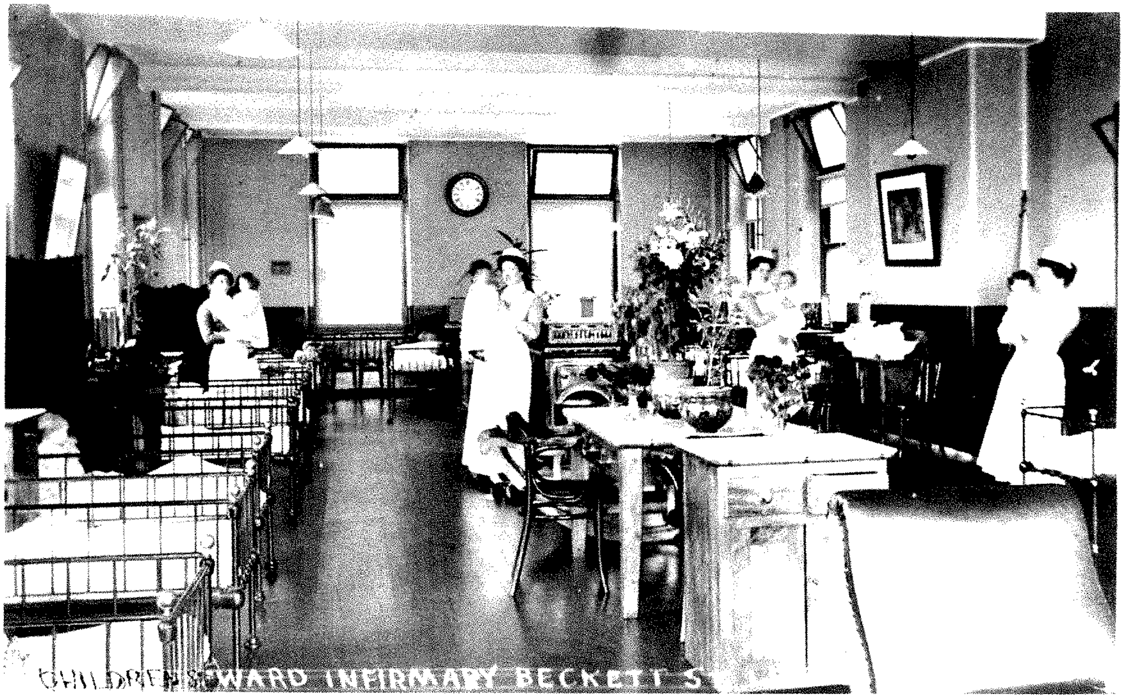
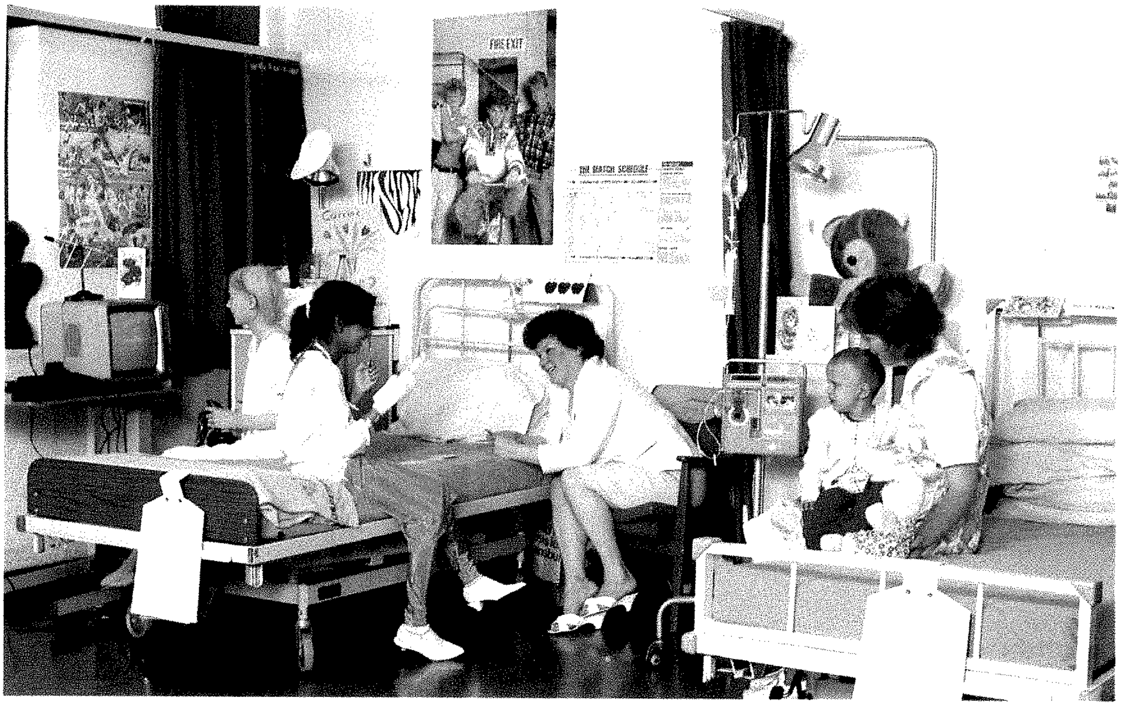
Additional help with this issue has been received from many sources. The Editors are particularly grateful to Geoffrey Davenport, Jean Gaffin, Deirdre McClarty, Marianne Meadow, Nigel Palmer, Cornelia Piper, Martin Valman, Thea Valman, Derek White, and the Departments of Medical Illustration at St James's University Hospital, Leeds, St Mary's Hospital Medical School, London, and Northwick Park.

Archives of Disease in Childhood, 1986, **61**, 990





A children's ward at St James's Hospital, Leeds, in the 1920s (top) and, below, a corner of a children's ward in the same hospital in 1986. (The girl on the left playing with a computer/video game has partial alopecia from cytotoxic therapy and the coloured girl to her right is attached to that standard appendage of the 1980s an intravenous line and infusion set.)

Archives of Disease in Childhood, 1986, **61,** 991–995

Original articles

Why do so many small infants develop an inguinal hernia?

T G POWELL, J A HALLOWS, R W I COOKE, AND P O D PHAROAH

Departments of Community Health and Child Health, University of Liverpool

SUMMARY Prevalence and incidence of inguinal hernia in a representative sample of low birthweight survivors were determined by tracing children at 3 years of age. Prevalence was examined in relation to perinatal factors recorded in hospital case notes, using a logistic regression model to allow for confounding variables.

Of the 1074 two year survivors, 995 (93%) were assessed. Seventeen per cent of 497 boys and 2% of 498 girls had a hernia by 3 years of age, a total cumulative prevalence of 9·2%: it was significantly increased by lower birth weight, male sex, neonatal intravenous feeding, and lack of respiratory disease. Neonatal illnesses were otherwise not associated with herniation, and most infants were well when they presented. Peak incidence was at the expected full term of gestation. Bilateral hernias were increasingly more common than unilateral hernias at lower gestational ages.

It is proposed that causes of increased abdominal pressure in healthy neonates are important causes of herniation during a critical period of inguinal development.

Inguinal hernia is the commonest indication for surgery in childhood, with a peak incidence in the first months of life.[1] Little is known about its aetiology, and its prevalence is not known, owing to the difficulties in tracing a large unbiased population.

Low birthweight infants have a higher prevalence of inguinal hernia in early childhood than other infants.[2] We investigated the incidence, prevalence, and clinical features of inguinal hernia in a large representative sample of low birthweight infants to give an indication of the surgical workload associated with increasing survival of low birthweight infants.

Low birthweight infants suffer far more perinatal illness than do other infants, but it is not known whether this accounts for their increased susceptibility to herniation. We used the data afforded by their close observation after birth to investigate which factors might be implicated in the aetiology of inguinal hernia in childhood.

Patients and methods

The sample comprised survivors of birth weight ≤2000 g born in 1979, 1980, and 1981 to residents of five health districts in Merseyside. It was derived from searches of birth notifications and admission registers of local maternity hospitals. Survivors were traced and, where possible, assessed in their homes. Presentation of inguinal hernia by 3 years of age was ascertained by history and examination and was verified by examining hospital follow up records. Questionnaires were sent to the parents and guardians of children who could not be visited at home.

Perinatal data were gathered from the case records of each hospital that cared for each mother and infant. Gestational age was recorded according to neonatal assessment if obstetric assessment was uncertain. Centiles of birth weight according to gestational age were derived from recent data. Hypertension in pregnancy was defined as recorded maternal diastolic blood pressure of more than 90 mm Hg. Mechanical ventilation was defined as support with continuous positive airways pressure or intermittent positive pressure ventilation for a minimum of 12 hours. Respiratory disease was defined as treatment with oxygen or mechanical ventilation, or both, for more than 24 hours, starting in the first week of life. Intravenous feeding was defined as the continuous use of intravenous amino acids for more than 24 hours during the neonatal period.

The SPSS-X[4] and GLIM[5] packages were used to analyse the data and check the accuracy of their collection. Confidence intervals were calculated using a continuity correction, and χ^2 tests for trends were calculated according to standard methods.[6] Variables were tested separately for degree and significance of association with inguinal hernia by tests appropriate for the type of variable: those used were the χ^2 with Yates's correction for 2×2 tables, the Mann-Whitney, and Student's unpaired t test.

Variables were tested for independent association with inguinal hernia if they were associated with it according to the univariate analyses (p about 0·1 or less). For this purpose a logistic regression model with presence and absence of inguinal hernia as the independent variable was used. The model allowed for the confounding effects of sex and birth weight, which were strongly associated with inguinal hernia according to the univariate analyses; it was decided to allow for birth weight rather than gestational age because its association with inguinal hernia was the stronger, their effects not being significantly additive. Different sequences and combinations of variables were tested to achieve the best model for estimating the probability of a hernia. Only variables that significantly improved the fit were included in this final model; thus these variables were significantly and independently associated with prevalence of inguinal hernia ($p<0{\cdot}05$).

Results

The sample. Of 1420 liveborn infants, 1074 survived to 2 years. Occurrence of inguinal hernia by 3 years was ascertained for 995 (93%) of the survivors, who form the sample. Children for whom there was insufficient information did not differ significantly from the sample in terms of birth weight, gestational age, sex, or neonatal illness.

Prevalence by sex, birth weight, and gestational age. (Table 1) Inguinal herniotomy was performed in 9·2% (95% confidence interval=7·6–11·3%) of the 995 survivors by 3 years and was twice as common as any other surgical procedure. There were no unoperated hernias. Prevalence increased significantly with decreasing birth weight or gestational age, but their effects were not significantly additive. Small for dates infants were not more likely to have a hernia than other infants. Boys had a higher prevalence of hernia than girls in every birth weight and gestational age group, with an overall relative risk of 9·2 to 1. Prevalence increased significantly with decreasing gestational age in both sexes.

Clinical features. Of 89 children for whom laterality was confirmed, 32 (36%) had a right sided and 15 (17%) had a left sided unilateral inguinal hernia. The 41 children (46%) with bilateral herniation included five who had had unilateral herniotomy with subsequent contralateral presentation. Bilateral hernias were increasingly more common than unilateral hernias at lower birth weights or gestational ages (Table 2).

Incidence peaked in the second month after birth (Table 3). Adjustment for the gestational age of each infant gives a peak incidence around the time of full term of gestation. Children with bilateral hernias presented earlier in relation to full term of gestation than did children with a unilateral hernia (p=0·018).

Eighty five per cent of the infants of birth weight

Table 1 *Numbers of children and prevalence of inguinal hernia (%) by 3 years of age, by sex, birth weight, and gestational age*

	Birth weight (g)										*All birth weights (% with hernia)*	
	501–1000		*1001–1250*		*1251–1500*		*1501–1750*		*1751–2000*			
	m	*f*	*m*	*f*	*m*	*f*	*m*	*f*	*m*	*f*	*m*	*f*
Gestation (weeks):												
25–27	5	13	7	3							50	6
28–30	8	12	30	23	29	29	13	7	1	4	21	4
31–33	4	1	14	8	31	34	48	41	72	53	17	2
34–36	2	1	5	6	17	19	39	49	108	108	14	1
>36			1	1	1	4	17	23	45	59	12	1
% With hernia:												
Male	37		23		21		17		12		17	*
Female		4		5		1		3		0		2
Both sexes	17·4		15·3		10·4		10·1		6·2			
(95% Confidence interval)	(8–32)		(9–24)		(6–16)		(7–15)		(4–9)			

m=Male, f=female.
Trend with gestational age: in males, p=0·009; in females, p=0·036.
Trend with birth weight: in males, p=0·001; in females, p=0·066.
*Sex difference: p<0·001.

Table 2 *Ratios of unilateral to bilateral hernias*

(a) According to gestational age

Hernia	*Gestational age (weeks)*				
	25–27	*28–30*	*31–33*	*34–36*	*>36*
Unilateral	3	5	16	15	9
Bilateral	3	15	14	8	1
Not known	1		1	1	

χ^2 For trend=9·84, p<0·005.

(b) According to birth weight

Hernia	*Birth weight (g)*				
	501–1000	*1001–1250*	*1251–1500*	*1501–1750*	*1751–2000*
Unilateral	2	4	8	14	20
Bilateral	5	11	9	9	7
Not known	1	–	–	1	1

χ^2 For trend=10·99, p<0·001.

Table 3 *No of children presenting with inguinal hernia* up to 3 years of age according to month after birth or after full term*

	Month											
	−3	*−2*	*−1*	*1*	*2*	*3*	*4*	*5*	*6*	*7–12*	*>12*	*All*
After birth:												
No				7	29	25	7	2	3	3	10	86
Cumulative %				8	41	70	78	81	84	87	100%	
After full term†:												
No	1	6	25	25	8	5	1	2	1	2	10	86
Cumulative %	1	8	37	66	75	81	82	84	85	87	100%	

Information was not available for six children with a hernia.
*For non-concurrent bilateral hernia, time of presentation of first hernia.
†Month after birth corrected for gestational age in each case.

>1500 g who developed a hernia presented after discharge home from neonatal care compared with only 40% of those of birth weight ≤1500 g (p<0·001). This is because most of the larger infants were discharged home before the age of peak incidence of herniation.

Initial presentation was invariably with a lump in the groin, often first noticed by parents and diagnosed by health visitors in the weeks after discharge from neonatal care. Two children presented during whooping cough infection. Diagnosis usually led to early surgery, but there was a delay of several months in four children who were at home. Six children had emergency herniotomy for irreducible incarceration, but we could not determine accurately how many other children developed incarceration.

Immediate post-surgical complications in 86 children included one case each of testicular infarction, scrotal abscess, and groin abscess. Five (5%) of the children had an ipsilateral recurrent hernia.

Prevalence of inguinal hernia was not significantly related to major forms of neurological disability such as cerebral palsy or educational subnormality.

Associations of perinatal factors with inguinal hernia. Factors not significantly associated with hernia in the univariate analysis included maternal age, marital state, social class, smoking, anaemia in pregnancy, antepartum haemorrhage, induction of labour, prolonged rupture of membranes, duration of labour, breech delivery, forceps delivery, multiple birth, birth order, hospital of birth, infant bruising, hypoglycaemia, malformation, duration of treatment with oxygen, pneumothorax, bacteraemia, fits, apnoeic attacks, and peak bilirubin concentration.

Some factors were associated with inguinal hernia by virtue of their association with birth weight: they were associated with hernia in the univariate analysis but not when allowing for birth weight in the regression analysis. They included gestational age, Apgar score at one minute, intubation at birth, day of full enteral feeding, duration of mechanical ventilation, treatment with theophylline, antibiotics, or indomethacin, necrotising enterocolitis, phototherapy, persistent ductus arteriosus, and intraventricular haemorrhage.

The best predictive model gave a risk of hernia that was inversely related to birth weight, with increased log odds according to sex (male:female=11·5:1), intravenous feeding (yes:no=3·1:1), and absence of respiratory disease (absent:present=2·4:1) (p<0·05 in each case). Although hypertension in pregnancy, a low Apgar score at five minutes, and hypothermia on admission to the neonatal unit were associated with increased prevalence of hernia when allowing for birth weight and sex (p<0·1), their effects on this final model were not significant.

The best models for predicting unilateral and bilateral inguinal hernias differed: birth weight was predictive only of bilateral hernias, while maternal hypertension (which included pre-eclampsia) was predictive of unilateral hernia. Mechanical respiratory support was not associated with increased prevalence of hernia but was predictive of bilateral rather than unilateral hernia when considering only those infants who did develop a hernia.

Discussion

The prevalence of inguinal hernia in children and adults is not known, but repair of inguinal hernia is the commonest operation performed by general surgeons on children[1] and men.[7] It is by far the commonest operation performed on low birthweight infants in early childhood.

Many hospitals have reported a high incidence of inguinal hernia in low birthweight survivors[8] after a report that 11 of 37 infants of birth weight ≤1000 g developed an inguinal hernia.[9] The prevalence of inguinal hernia by 6 months of age is significantly higher in infants born before 37 weeks' gestation than in full term infants.[2] Our data confirm that prevalence of inguinal hernia, in particular of bilateral hernias, increases with lower birth weight or lower gestational age. Numbers with bilateral hernias may have been overestimated owing to contralateral exploration in cases of left sided hernia, but others have also reported that bilateral hernias are common in preterm infants.[2 10 11]

Prevalence of inguinal hernia was similar among the 223 twins and the singletons in the sample. The reported higher prevalence in twins than singletons[12] did not allow for birth weight, but the mean of the reported birth weights for twins was less than 2500 g.

Inguinal hernia is hazardous in infancy, when the rate of incarceration may be over 25%;[10 11] it is the commonest cause of intestinal obstruction between 1 week and 4 months.[13] Testicular infarction is more common after emergency surgery.[11 14] Rates of recurrence of hernia in children are higher after bilateral herniotomy and emergency surgery,[11] and our data suggest that recurrence is common in low birthweight infants. Postoperative pulmonary complications and episodes of apnoea are common in preterm infants.[15] We found few serious sequelae of inguinal hernia, but this is a tribute to standards of care rather than a cause for complacency.

The dilemma of whether to explore the other side of the unilateral hernia in infants[16] may be relevant to low birthweight infants in particular. Bilaterality increases with lower birth weight or gestational age, especially in infants who are ventilated mechanically.

The aetiology of inguinal hernia must relate to a defect in the abdominal wall and a force sufficient to propel viscera through it. Clearly, a lesser force is necessary with a larger or more distensible defect.

The nature of the defect in adults is controversial,[17] but herniation in infants is through the processus vaginalis.[1] This peritoneal pouch descends in the eighth or ninth month of gestation into the scrotum ahead of the testis or into the labium. It usually closes and atrophies some time after birth, although postmortem studies have shown a persistent processus vaginalis in 80–94% of neonates, 57% of 1 year olds and 15–37% of adults.[1] Herniography has shown a contralateral persistent processus in 63% of infants with unilateral hernia before 2 months, declining to about 40% at 2 years and beyond, of which a high proportion develop a hernia on the side of the persistent processus some time in life.[16] The role of the processus vaginalis in determining herniation at any age is not clear, however, because there is no available non-invasive technique for its prospective study in those without a demonstrable hernia. The low relative risk of inguinal hernia in very preterm girls implies that a persistent processus vaginalis is not the sole anatomical factor that determines herniation. Similarly, congenital anomalies and increased abdominal pressure do not increase frequency of patency of the processus but are associated with increased frequency of bilateral hernias.[18]

The inguinal canal is very short in infancy, and the external ring is almost directly over the internal ring,[1] which presumably facilitates testicular descent. Failure of testicular descent, and thus orchidopexy, is associated with inguinal hernia.[1] The right testis descends later than the left testis: inguinal hernia is commoner on the right than the left side. In very preterm infants neither testis is fully descended at birth: bilateral hernias are increasingly common with lower gestational age. This suggests that inguinal hernia results from birth during a critical period when developing inguinal anatomy facilitates herniation on both sides. The peak age at presentation by the expected full term of gestation is consistent with this hypothesis, as is the earlier presentation of bilateral compared with unilateral hernias in relation to full term of gestation.

Most preterm infants, however, do not get a hernia, so that non-anatomical factors may be important in determining which ones do. Other data also suggest that respiratory disease and treatment do not increase susceptibility to herniation: 8·2% of 73 ventilated infants of birth weight <1501 g who survived to 24 months of age developed a hernia[19] compared with 8·7% of 172 unselected survivors of similar birth weight who developed a hernia by 6 months of age.[20]

A relation with growth retardation was not apparent within the low birthweight range, although low birthweight infants born at full term had a high prevalence of inguinal hernia. There was no evidence that prenatal factors were important determinants of bilateral hernias when allowing for birth weight and sex, although maternal hypertension seemed to increase susceptibility to unilateral hernia.

Intravenous feeding was routine in sick neonates and may have been a marker for a factor not included in the analysis, such as weight loss or abdominal distension. Neonates with conditions associated with abdominal destension have an increased incidence of inguinal hernia.[10 18] Necrotising enterocolitis was diagnosed in 31 infants, seven of whom developed a hernia. This proportion was higher than for infants without necrotising enterocolitis by univariate analysis (p=0·02). Necrotising enterocolitis did not contribute to prediction of inguinal hernia when allowing for other variables, but this may have been due to the fairly small number of children who had necrotising enterocolitis.

Other than the relation with intravenous feeding, there were no significant relations between neonatal illnesses and inguinal hernia, and most infants were healthy at presentation. Precipitation of an inguinal hernia must relate to increased abdominal pressure and occurs in the absence of respiratory or other disease in most infants. It is conceivable that the large volumes of milk given to healthy underweight infants contribute to herniation (most receive an adult equivalent for weight of more than three gallons a day). Enteral feeding, vigour, and healthy lungs may precipitate herniation in immature infants, in whom inguinal anatomy is designed for testicular descent in the calm of life in utero.

The incidence of inguinal hernia in all children is highest in the neonatal period.[1] If preterm infants develop a hernia because they are born before inguinal development is normally complete other infants may do so because their inguinal development is abnormally incomplete at full term, whether governed by genetic or other factors.

We are grateful to Mr R E Cudmore for advice given during the preparation of this work.

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Intrauterine supraventricular tachyarrhythmias and transplacental digitalisation

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SUMMARY Six newborn infants with intrauterine supraventricular tachyarrhythmias (five cases of atrial flutter and one of supraventricular tachycardia) are described. Transplacental digitalisation was attempted in three cases. Supraventricular tachycardia associated with hydrops fetalis, detected in a fetus at a gestation of 31 weeks, was successfully converted to normal sinus rhythm eight days after the mother began treatment with digoxin. The serum concentration of digoxin in cord blood almost equalled the maternal concentration in three cases.

In the remaining three cases treatment with digitalis was effective in converting tachyarrthmias to sinus rhythm after delivery.

With maintenance digoxin therapy, the prognosis of fetal tachyarrhythmias seems to be good, once conversion to sinus rhythm has been accomplished.

Fetal tachyarrhythmias have been cited as possible causes of non-immune hydrops fetalis and intrauterine fetal death.[1] Transabdominal fetal electrocardiography is fraught with difficulty and therefore of limited value in the analysis of fetal cardiac arrhythmias. On the other hand, fetal echocardiography is a non-invasive means of not only diagnosing fetal cardiac structural anomalies and rhythm disturbances but also detecting associated congestive heart failure in utero.[2–5]

A number of authors have reported success with transplacental pharmacological treatment to convert intrauterine supraventricular tachyarrhythmias to a normal sinus rhythm.[3 6–14] In such cases fetal echocardiography is a useful tool for serial monitoring of cardiac rhythm and evaluation of antiarrhythmic treatment.

There have been only a few reports on fetal tachyarrhythmias and transplacental pharmacological treatment in several cases.[15–17] This report describes the clinical course of six newborns with intrauterine supraventricular tachyarrhythmias and, in three cases, the results of transplacental digitalisation.

Patients and methods

Between 1977 and 1985 six newborn infants with intrauterine supraventricular tachyarrhythmias were admitted to our hospitals and were given antiarrhythmic treatment (Table 1).

In three cases, after the obstetricians had detected fetal tachycardia, fetal echocardiography was performed, and the mothers received antiarrhythmic agents.

Fetal echocardiography was performed trans-

Table 1 *Clinical findings of the six cases*

Case No	*Sex*	*Gestational age on recognition (weeks)*	*Fetal heart rate (beats/min)*	*Tachyarrythmias*	*Congestive heart failure*
1	M	39 (19 hours antepartum)	180–200	Atrial flutter	(+)
2	M	40 (two hours antepartum)	200	Atrial flutter	(+)
3	M	38 (intrapartum)	210	Atrial flutter	(+)
4	M	30	240	Atrial flutter	Hydrops fetalis
5	M	41 (one day antepartum)	80–200	Atrial flutter	(−)
6	F	31	300	Supraventricular tachycardia	Hydrops fetalis

abdominally with a 5 MHz linear transducer. An M mode study was performed to evaluate disturbances in cardiac rhythm after two dimensional echocardiographic analysis of the cardiac structures—cardiac chambers, interventricular and interatrial septa, and atrioventricular and semilunar valves, which could be readily obtained.

The P wave of the surface electrocardiogram represented A wave of the fetal atrioventricular valves, and the QRS wave complex was shown as atrioventricular closure or semilunar valve opening. The cardiac phases could be presumed by motion of the cardiac walls or valves.

The diagnosis of the fetal arrhythmias was made mainly by the motion of these cardiac structures.

Five of the six newborn infants were boys, and all were full term (38–41 weeks' gestation).

Results

In four cases the fetal tachyarrhythmia was first recognised shortly before birth or during delivery.

In case 2 fetal tachycardia with a heart rate of 200 beats/minute was first noted at 40 weeks' gestation. In the belief that the fetus was distressed the obstetrician performed caesarean section. An electrocardiogram recorded immediately after birth showed atrial flutter with 2:1 atrioventricular conduction.

In case 5 a fetal irregular rhythm with a rate of 80 to 200 beats/minute was first noted one day before birth. A fetal echocardiogram showed artrial flutter with 2:1 to 5:1 atrioventricular conduction. Hydrops fetalis was not detected.

In cases 4 and 6 hydrops fetalis with massive ascites, pleural effusion, and subcutaneous oedema was present at gestational weeks 30 and 31, respectively. Case 6 had no oedema on delivery, however, because the supraventricular tachycardia had reverted to normal sinus rhythm before delivery as a result of transplacental digitalisation.

Table 2 *Serum concentration of digoxin in cases 4, 5, and 6*

Case No	*Gestational age (weeks)*	*Digoxin dose on delivery (mg/day)*	*Serum concentration of digoxin (ng/dl)*	
			Maternal blood	*Cord blood*
4	30	0·5 (oral)	1·00	0·62
5	41	0·5 (intravenous)	1·20	1·30
6	31	0·25 (oral)	0·30	0·36

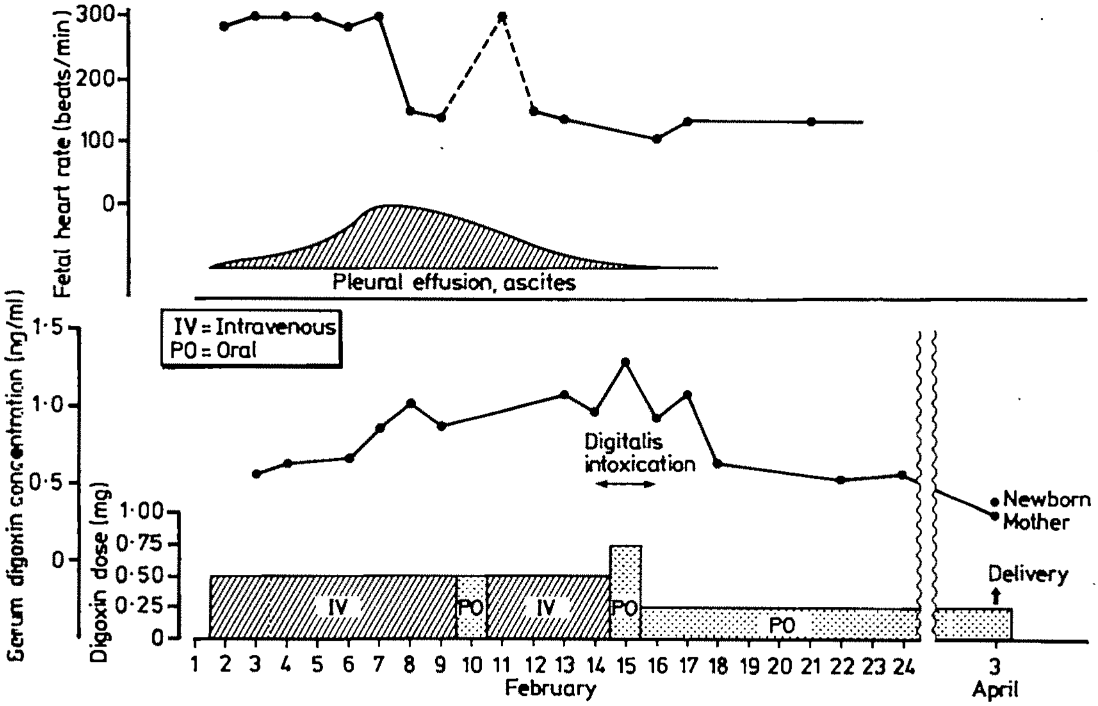

Fig. 1 *Clinical course of case 6.*

Fetal echocardiography disclosed atrial flutter with 2:1 atrioventricular conduction at a heart rate of 240 beats/minute in case 4 and supraventricular tachycardia with 1:1 atrioventricular conduction at a heart rate of 300 beats/minute in case 6.

Shortly after birth, cases 1, 2, and 3 had evidence of mild cardiomegaly on chest radiographs and moderate hepatomegaly. No signs of congestive heart failure were observed in case 4 in the perinatal period.

Structural abnormalities were ruled out by postnatal echocardiography and electrocardiography in all cases.

Treatment with digoxin was begun immediately after diagnosis of supraventricular tachycardia. Emergency injections of digoxin were administered to three infants (cases 1, 2, and 3) after delivery. The atrial flutter stopped 20 minutes after injection of digoxin in case 1 but persisted for two days in case 2 and five days in case 3.

Transplacental digitalisation was attempted in three cases (cases 4, 5, and 6). In case 4 fetal tachyarrhythmia was detected at 30 weeks' gestation and hydrops fetalis developed at 34 weeks. Transplacental digitalisation was attempted and atrial flutter converted briefly to a sinus rhythm. Atrial flutter returned, however, and persisted, without improvement of hydrops fetalis. Caesarean section was performed at 36 weeks' gestation. The serum concentration of digoxin in cord blood is shown in Table 2. Successful electrical cardioversion to a sinus rhythm was achieved immediately after birth. In case 5 fetal tachyarrhythmia was detected at 41 weeks' gestation. Although the mother was digitalised for two days, atrial flutter persisted, but it spontaneously converted to sinus rhythm, however, 10 minutes after normal delivery.

Case 6. The details of the clinical course of case 6 are as follows (Fig. 1).

At 31 weeks' gestation a 27 year old primigravida noticed a sudden decrease in fetal movement. Her obstetrician noted fetal tachycardia and referred the patient to our hospital.

Fetal echocardiography performed on the same day revealed fetal tachycardia of 300 beats/minute with 1:1 atrioventricular conduction (Fig. 2). There was no cardiac structural abnormality, and scalp oedema and ascitic fluid were absent.

Digoxin (0·25 mg twice a day intravenously) was administered to the mother. On the day after admission fetal echocardiograms showed persistent supraventricular tachycardia and a small amount of ascitic fluid and pleural effusion. On the sixth day massive ascites, pleural effusion, and subcutaneous oedema were present (Fig. 3). A brief episode of normal heart rate (130 beats/minute) occurred on the seventh day, when the maternal serum digoxin concentration was 1·02 ng/ml. Intravenous administration of digoxin was changed to oral administration on the eighth day, and the normal sinus rhythm returned to tachycardia. Shortly after intravenous digitalisation was restarted, the tachycardia converted to normal sinus rhythm, which continued thereafter.

Fetal echocardiography showed complete resolution of hydrops fetalis one week after normal sinus rhythm was established. The mother complained of

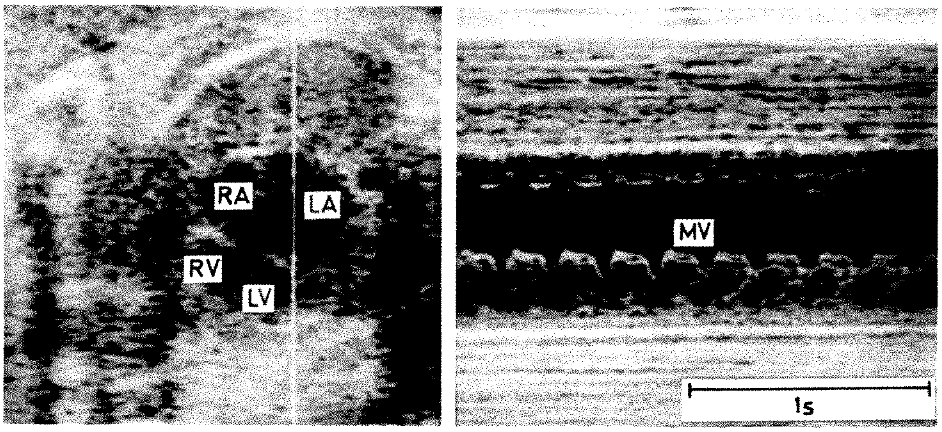

Fig. 2 *Two dimensional and M mode echocardiogram from case 6 on the first hospital day. Rapid motion of the mitral valve shows atrial and ventricular rates of 300 beats/minute. No pleural effusion was present. LA: Left atrium; RV: right ventricle; RA: right atrium; RV: right ventricle; MV: mitral valve.*

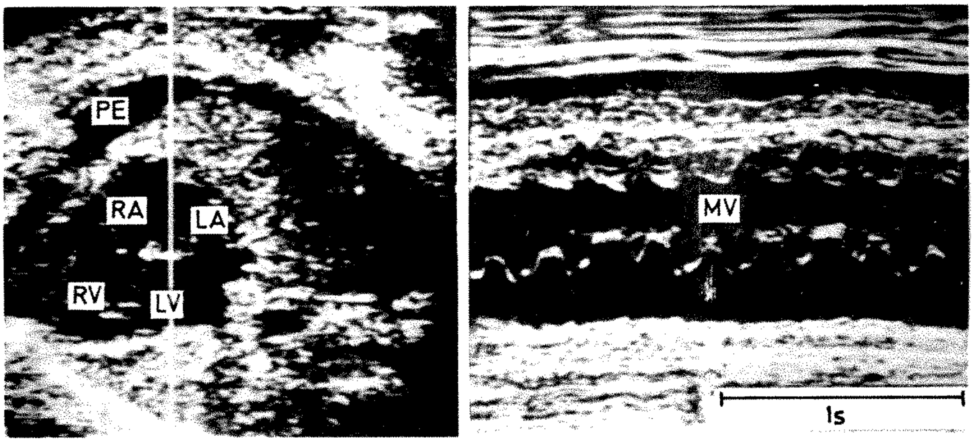

Fig. 3 *Two dimensional and M mode echocardiogram from case 6 on the sixth hospital day. Massive pleural effusion was present. LA: Left atrium; RV: right ventricle; RA: right atrium; RV: right ventricle; MV: mitral valve, PE: pleural effusion.*

palpitations on the 13th day of admission to hospital, and her electrocardiogram showed Wenckebach second degree atrioventricular block and digitalis effect of ST-T. These phenomena were considered to be due to digitalis intoxication. Maternal serum digoxin concentration was 1·29 ng/ml. Digoxin intoxication subsided after the oral dosage was reduced to 0·25 mg once a day. The patient was discharged at this dosage, and there was no recurrence of fetal tachycardia. A girl weighing 3791 g was delivered vaginally at 40 weeks' gestation.

The serum concentrations of digoxin in the umbilical cord blood and maternal blood on delivery were 0·36 ng/ml and 0·30 ng/ml, respectively. The infant's electrocardiogram showed Wolff-Parkinson-White syndrome (type A) and no structural defect was observed by echocardiography. Prophylactic digoxin has been administered for one year without recurrences of supraventricular tachycardia.

Discussion

Before the era of fetal echocardiography, tachyarrhythmias occurring in utero were often interpreted as fetal distress, and often caesarean sections or prematurely induced labour were performed.[18]

Recent development and improvement of fetal echocardiography has made it possible to study fetal cardiac structure, monitor fetal rhythm disturbance, and administer appropriate transplacental pharmacological treatment.[15]

Newburger *et al* reported that congestive heart failure was evident, at birth or shortly after birth, in 62% of infants with intrauterine supraventricular tachycardias.[15] Deaths due to intrauterine tachycardias have also been reported.[3 5 11]

To our knowledge, successful pharmacological cardioversion has been achieved in about 10 cases (Table 3).[3 6–14] In most of the successful cases,

Table 3 *Reported cases of successful transplacental pharmacological cardioversion*

	Year of publication	*Gestational week*	*Tachyarrhythmia*	*Antiarrhythmic agent*
Teuscher[14]	1978	34	Tachycardia (>200 beats/min)	Propranolol
Kerenyi	1980	29–30	Supraventricular tachycardia	Digoxin
Lingman[12]	1980	29	Supraventricular tachycardia	Digoxin
Harrigan[7]	1981	26	Tachycardia (>260 beats/min)	Digoxin
Dumesic[6]	1982	26	Tachycardia (>240 beats/min)	Digoxin Propranolol Procainamide
Kleinman[4]	1982	27	Supraventricular tachycardia	Digoxin
Heaton[8]	1982	30	Supraventricular tachycardia	Digoxin
Kleinman[11]	1983	35	Supraventricular tachycardia	Digoxin
Iliff[10]	1983	36	Tachycardia	Digoxin
Hirata[9]	1985	34	Atrial flutter	Digoxin
Present study	1985	31	Supraventricular tachycardia	Digoxin

digoxin was administered to the mothers because it has been confirmed that digoxin crosses the placenta and that the fetal serum digoxin concentration approximates to that of the mother.[19] A few cases of fetal tachycardias treated successfully with propranolol[15] or procainamide[6] have been reported. In newborn babies, however, the possible side effects of propranolol include depressed Apgar scores, hypoglycaemia, and episodes of bradycardia,[20] and therefore propranolol is not the drug of first choice for fetal supraventricular tachycardias. The effects of other drugs, such as procainamide and verapamil,[10] have not been confirmed, because they have been administered to only a few patients.[6 9 14]

In three cases of intrauterine tachyarrhythmias we attempted to convert atrial flutter and supraventricular tachycardia to normal sinus rhythm by administering digoxin. In case 6 fetal supraventricular tachycardia recovered on administration of digoxin to normal sinus rhythm in utero and did not recur until birth.

Although digoxin prevented atrial flutter temporarily in case 4, atrial flutter recurred and the mother underwent caesarean section at 36 weeks' gestation.

It is easier and safer to treat supraventricular tachycardia after than before delivery, because we have better methods for postpartum treatment, including electrical cardioversion and precise pharmacological monitoring. When an immature fetus with supraventricular tachycardia has a poor chance of extrauterine survival, however, due to immaturity, transplacental pharmacological cardioversion should be attempted.

Because of the potential risk of congestive heart failure in utero, we attempted transplacental digitalisation in case 5, but extrauterine treatment might have been more appropriate as the fetus was full term.

Once fetal atrial supraventricular tachyarrhythmia had been converted to normal sinus rhythm, no patient in our series experienced recurrent tachyarrhythmia during the first year of life with preventive administration of digoxin. As the prognosis of these supraventricular tachyarrhythmias seems to be good, preventive treatment is recommended for a minimum of one year.

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Congenital leukaemia: an unusual cause of stillbirth

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SUMMARY Three cases of congenital leukaemia associated with hydrops and intrauterine death are described. The leukaemic infiltrates, which involved both the infants and the placentas, were of monocytic, lymphoblastic, and myeloblastic types, respectively. The general lack of recognition of the condition is probably due to inadequate histological examination of the stillborn infant and the placenta.

Although rare, congenital leukaemia is a condition well recognised by haematologists and paediatricians. From what is known of the kinetics of leukaemic cell generation,[1] the leukaemic process in affected infants must have been present for some months in utero. This indicates that congenital leukaemia could be a cause of stillbirth, but a search of the published reports has revealed only four recorded cases of such an association.[2-5] The paucity of published cases suggests that the diagnosis is missed by the pathologist. This is not surprising in view of the low autopsy rate in stillborn infants and the generally poor standard of histopathological examination accorded to such cases.

Two of the three cases described in this report occurred in a single year in the Grampian region of Scotland, while the third was seen several years before in Leeds, England. This third case has been annotated previously,[6 7] although with no detailed descriptions.

Case reports

Case 1. The 21 year old mother was of blood group A, rh D positive and Venereal Disease Research Laboratory (VDRL) negative. Her one previous pregnancy was uneventful, resulting in the birth of a normal child with a birth weight of 3160 g, who was still alive and well. During the present pregnancy she was in good health until 24 weeks' gestation when she developed a monilial vaginitis, which was successfully treated by Clotrimazole Vaginal Tablets. At roughly 34 weeks' gestation the patient noticed that fetal movements had stopped: two weeks later intrauterine death was confirmed by ultrasound examination. After an induced labour she delivered a female stillborn infant weighing 2400 g. Postpartum viral studies on the maternal serum excluded recent infection with a variety of viruses, including cytomegalovirus and herpes

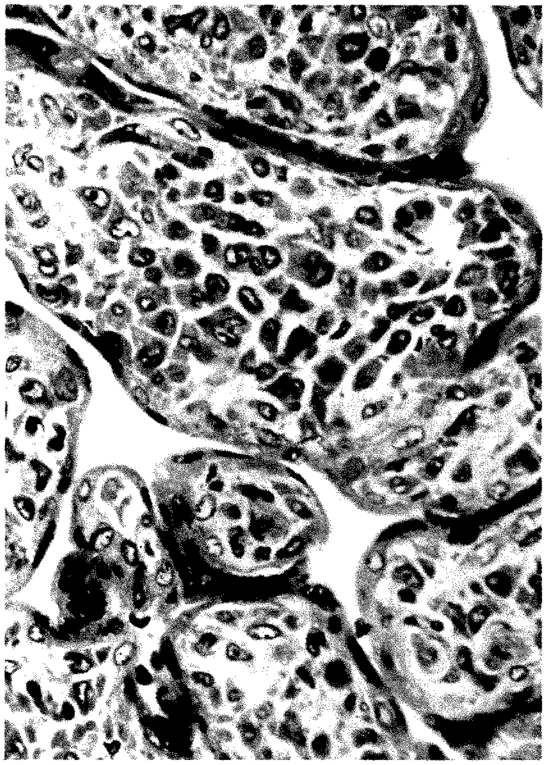

Fig. 1 *Chorionic villi in case 1 expanded by histiocytic cells, showing mitotic activity (haematoxylin and eosin staining).*

simplex. The toxoplasma dye test also yielded negative results.

At autopsy on the same day the infant showed mild hydrops and advanced maceration: body weight was 2320 g, indicating some fluid loss from the tissues. Foot length was 7·0 cm. There were no external or internal malformations. The liver (which weighed 80 g), spleen (10 g), adrenals (3 g), and kidneys (10 g) were unremarkable. The pleural surfaces of both lungs, however, were diffusely covered by a thin white lesion arranged in a fine reticular pattern. The placenta, which weighed 765 g, was abnormally firm and fleshy. The fetal surface showed several firm pale subchorionic plaques up to 2 cm in diameter, and the cut surface of the placenta was uniformly pale.

Histology of the placenta showed the chorionic villi to be greatly expanded, with a highly cellular stroma due to diffuse infiltration by fairly uniform cells with large often indented nuclei, a moderate amount of faintly eosinophilic cytoplasm, and a high mitotic rate (Fig. 1). Permeation of the lumina of both the stromal capillaries and of the larger stem vessels by these cells was extensive, but there was no evidence that the trophoblast basement membrane had been breached, and the abnormal cells were not found in the intervillous space nor in the adjacent decidua. Due to advanced autolysis, histological detail of the fetal viscera was poor, but it could be seen that the reticular pattern on the pleura was due to extensive infiltration of lymphatics by cells of similar appearance to those infiltrating the placental stroma and vessels. A similar infiltrate was detected in the liver, spleen, and periadrenal and pericardial fat.

To confirm the initial impression that these cells were histiocytes, immunoperoxidase studies were performed, using the peroxidase antiperoxidase method with antisera to κ and λ light chains, IgM, IgA, IgG, and IgD heavy chains, muramidase activity, and α_1 antitrypsin concentration. The last two antiserum samples produced the pattern of granular paranuclear staining typical of monocytic-histiocytic neoplastic cells (Fig. 2). Electron microscopy of the placenta confirmed the monocytic/histiocytic nature of the infiltrate, showing numerous primary and secondary lysosomes, with occasional residual bodies (Fig. 3). The cell borders were rather irregular, with a few microvillous projections, and the vesicular nucleus tended to contain a single nucleolus. These histiocytes did not have the cytoplasmic Birbeck granules described in malignant histiocytes of Langerhans' type.

The light microscopic, immunohistochemical, and ultrastructural appearance all indicated, therefore, that these cells were monocytic (histiocytic) in nature and that this was a case of monocytic leukaemia.

Unfortunately, chromosomal analysis was unsuccessful in this infant.

Case 2. The mother was 26 years of age, blood group rh D positive and VDRL negative. Her two previous pregnancies had been normal, resulting in healthy infants weighing 3500 g and 3770 g at term. During the present pregnancy all went well until the 26th

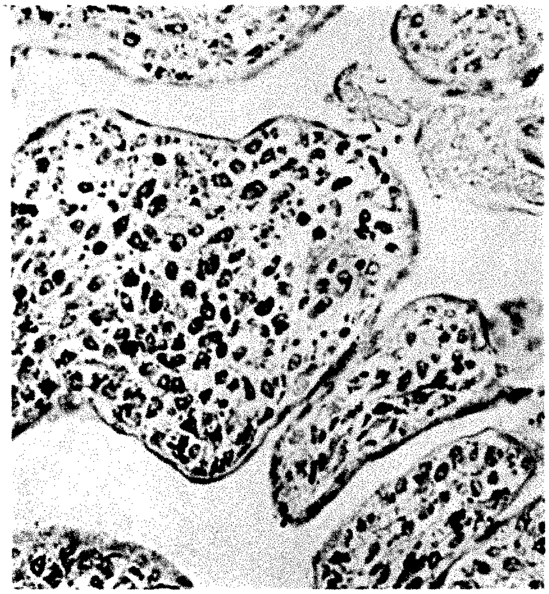
Fig. 2 *Heavy cytoplasmic staining for muramidase activity in tumour cells in case 1 (immunoperoxidase staining).*

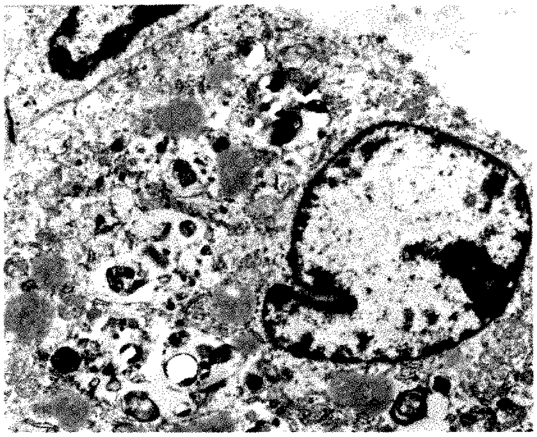
Fig. 3 *Electron microscopy of tumour cell in case 1, showing lysosomes and residual bodies.*

week of gestation, when she had what she thought was mumps. For the next two months she had several 'flu like' illnesses. At 34 weeks' gestation she developed premature labour and spontaneously delivered a male stillborn infant weighing 2400 g. Viral antibody titres in the maternal serum showed no evidence of infection with any of the viruses tested, including mumps, influenza A and B, cytomegalovirus, and herpes simplex. The toxoplasma dye test also yielded negative results.

At autopsy the infant showed moderate maceration and mild generalised hydrops with abdominal distension. The palmar creases were normal and no other external abnormality was noted. The placenta had weighed 800 g at delivery, but now weighed 550 g and presented a most unusual appearance, in that the surface vessels running in the chorionic plate to the insertion of the cord were distended by firm yellow 'thrombus' (Fig. 4). Sectioning of the placenta showed that the larger villous stem vessels were also involved. All three vessels of the umbilical cord contained inspissated material, but this was pinkish and more pultaceous, presumably due to autolysis. The pericardial, pleural, and peritoneal cavities contained an increased amount of fluid, which was turbid, a finding unusual in maceration. The pleural surfaces of the lungs were studded with small pale plaques. The most striking feature, however, was that the entire fetal vasculature, including the cerebral vessels, contained pultaceous material similar to that in the umbilical vessels. The cardiac chambers were also distended by this material. The right and left lungs weighed 13 and 17 g, respectively, and the heart was slightly enlarged at 20 g. There was moderate hepatosplenomegaly (liver 120 g and spleen 10 g). The other organs were normal in weight (kidneys 17 g and adrenals 4 g) and appearance.

Histology showed the intravascular material to be blood in which 80–90% of the cells were of the white cell series, most apparently being of an undifferentiated blast form (Fig 5 (a) and (b)). The liver and spleen were infiltrated by these cells and there was extensive involvement of the myocardium (Fig. 6), pericardial fat, and pulmonary lymphatics. In the placenta these hyperchromatic cells were confined to the vascular lumina and were not present within the stroma, intervillous space, or decidua.

By light microscopy alone it was not possible to determine whether these cells were myeloblasts or lymphoblasts. Electron microscopy, however, indicated that the cells were of lymphoid origin (Fig. 7). There was a high nuclear:cytoplasmic ratio, the euchromatin nuclei being rounded or ovoid with occasional deep indentations. There were usually two or more nucleoli. The cytoplasm was packed by polyribosomes and none of the cells contained granules. Immunoperoxidase studies, performed as in case 1, yielded negative results.

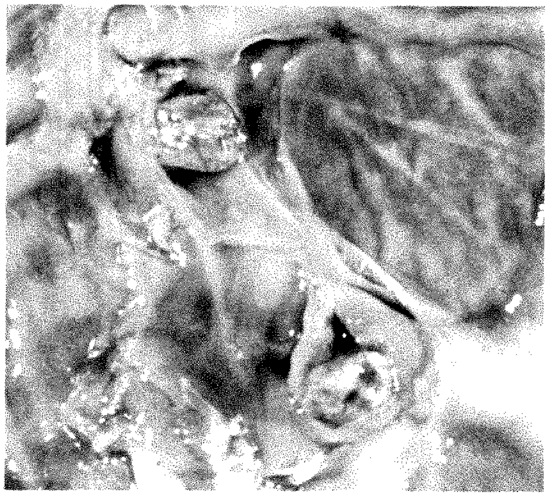
Fig. 4 *'Thrombus' protruding from chorionic vessels at cord insertion site in case 2.*

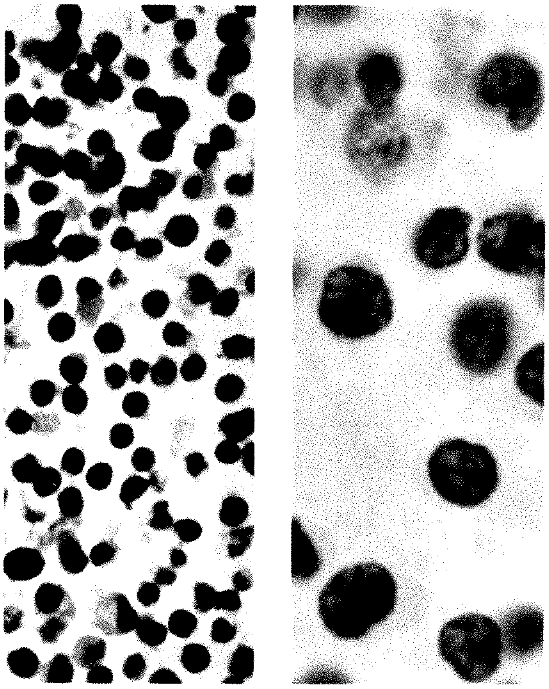
Fig. 5 (a) and (b) *Undifferentiated blast cells in 'thrombus' in case 2 (haematoxylin and eosin staining).*

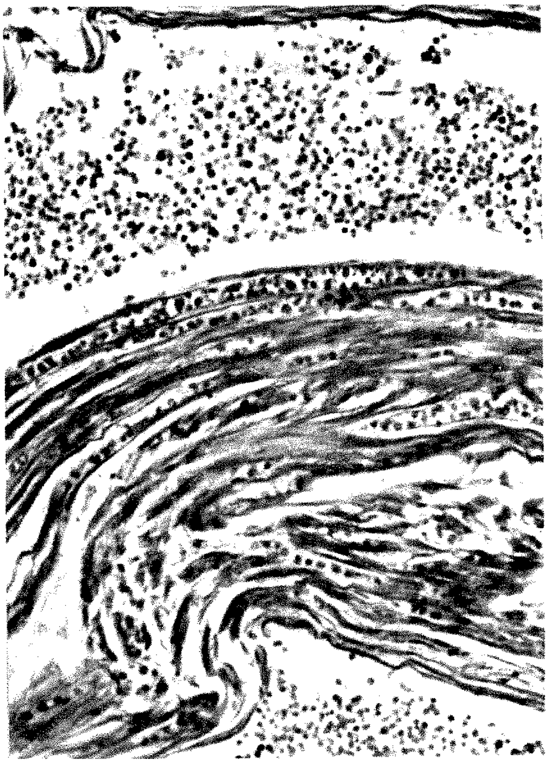

Fig. 6 *Infiltration of myocardium by tumour cells in case 2 (haematoxylin and eosin staining).*

On the basis of the ultrastructural appearances, it was concluded that the infiltrating cells were lymphoblasts and that this infant had had a lymphoblastic leukaemia. Chromosomal analysis showed a 47, XY+21 karyotype—that is, Down's syndrome.

Case 3. This case has not been previously described, although photomicrographs of the placenta from this baby have been used by Fox[6] and Becker[7] as an example of congenital leukaemia.

The mother was 24 years old, blood group A, rh D positive and VDRL negative. This was her first pregnancy. Viral titres carried out early in pregnancy revealed a raised titre to rubella at 1 in 256, but nothing else of note. The pregnancy continued normally until 35 weeks' gestation when she developed premature labour and delivered a slightly macerated stillborn male infant weighing 2010 g. A toxoplasma dye test at that time showed a titre of less than 1 in 8. A specimen submitted for evidence of infection by herpes virus also yielded negative results.

At autopsy the male infant weighed 1825 g and was moderately hydropic. There were no other external abnormalities and the internal viscera, although showing liquefaction, were normal. The placenta was normal in appearance and weighed 475 g. The tentative diagnosis made at autopsy was idiopathic hydrops fetalis. Histology of the placenta showed the villous stroma to be uniformly and densely infiltrated by hyperchromatic, poorly differentiated cells (Fig. 8). No such cells were found in the intervillous space or in the attached decidua.

The umbilical cord vessels were not involved. Although staining of the lungs was poor due to autolysis, it could be seen that the veins and lymphatics were engorged with hyperchromatic nucleated cells similar to those present in the placental villi. The exact nature of these cells could not be determined, but their morphology suggested they were probably immature precursors of the myeloid series and that this was a case of myeloblastic leukaemia.

Chromosomal analysis of fetal tissue was unavailable.

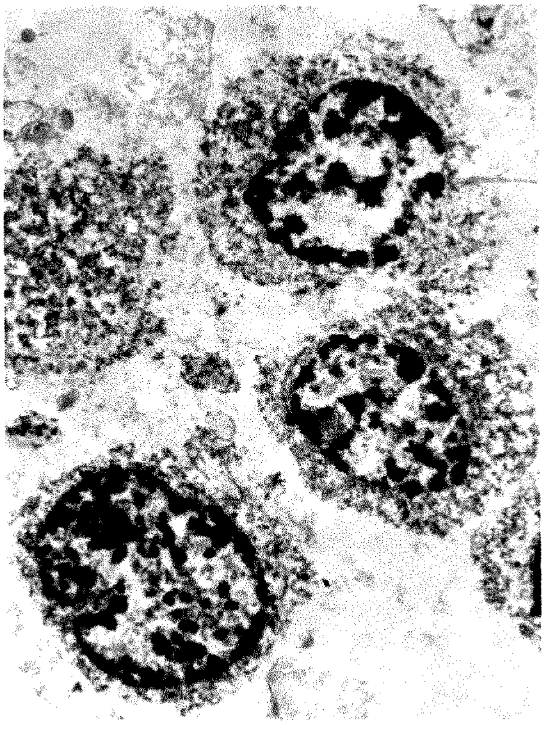

Fig. 7 *Electron microscopy of blast cells in case 2, showing lymphoid characteristics.*

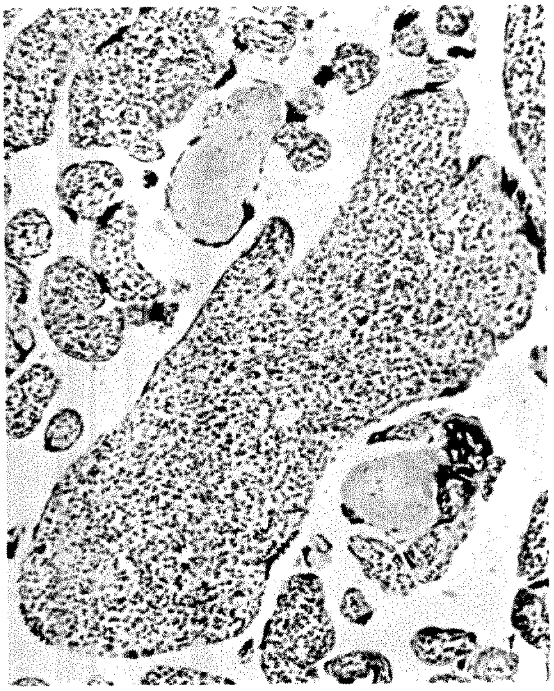

Fig. 8 *Dense cellular infiltration of chorionic villi in case 3 (haematoxylin and eosin staining).*

Discussion

In each of these three stillborn infants there was widespread visceral infiltration by cells of a uniform neoplastic appearance. In cases 1 and 3 there was also involvement of the placental stroma but no extension of the tumour cells into the intervillous spaces or maternal decidua. These cells did not metastasise from a primary solid tumour of the fetus. In case 1 both the ultrastructural and immunohistochemical features indicated that the cells were monocytic/histiocytic in origin. In case 2 the cells were less well preserved, but electron microscopy showed that the primitive blast cells were lymphoblasts rather than myeloblasts. In case 3 ultrastructural and histochemical studies were not available, but the infiltrating cells seemed to be of the primitive myeloid series. Because of the nature of the proliferating cells and the massive widespread visceral infiltration of non-haemopoietic organs and vascular involvement, we believe these three stillborn infants had forms of true congenital leukaemia. The possibility that case 1 was an example of malignant histiocytosis was considered, but the cellular infiltrate was more uniform than that found in histiocytosis, there was no erythrophagocytosis, and the ultrastructural features were not those described in histiocytosis X.

Congenital leukaemia is a rare condition, about 100 cases of which have been published[8] In many of the early cases the diagnosis was probably incorrect, a point made by Pierce in her review of the cases published.[9] Some authors believe that congenital leukaemia does not exist and that all the cases reported as such were examples of other fetal or neonatal haematological disorders.[10] The reason for their scepticism is that the fetus and neonate readily produces a leucoerythroblastic or leukaemoid reaction to a variety of stimuli, including severe haemolysis (as in erythroblastosis fetalis) and congenital infection. This leukaemoid reaction can easily be mistaken for a true leukaemia, both on the peripheral blood films (where the white blood cell count can reach $114 \times 10^9/l$) and on examination of tissue at autopsy.

We feel that we can exclude the possibility of the leukaemoid reaction in these infants on both serological and histological grounds. In the past erythroblastosis fetalis was occasionally mistaken for congenital leukaemia. All three mothers of these infants were rh positive and showed no irregular blood group antibodies on routine serology. Although Coombs tests were not carried out on fetal blood, the infants did not show either the macroscopic or microscopic appearances of severe intrauterine haemolysis. The degree of hydrops was only mild to moderate and the macroscopic visceral changes seen in erythroblastosis fetalis[11] were not present. There was no histological evidence of chronic fetal red cell destruction, and nucleated red blood cells were not increased.

The leukaemoid reaction can also be produced by intrauterine fetal infections such as syphilis, cytomegalic inclusion disease, rubella, toxoplasmosis, and herpes simplex. Antibodies were not detected to these infective agents in any of the three cases and there was no evidence at autopsy that the fetuses had suffered from any of these conditions.

Septicaemia can produce grossly raised white blood cell counts.[12] Bacteriological cultures made from lung and spleen revealed a scanty *Escherichia coli* on enrichment in case 1 and a similar scanty growth of coagulase negative *Staphylococcus*, but again only in enrichment, in case 2. Both these isolates were probably contaminants. There was no histological evidence of pneumonia or chorioamnionitis in any of the three cases.

Neonates with chromosomal anomalies, particularly those with a trisomy of chromosome 21 (Down's syndrome), often have a congenital or neonatal myeloproliferative disorder, which can be indistinguishable from acute myelogenous leukaemia.[13] It has been described as 'congenital transient acute leukaemia'[14] and is probably an ineffective regulation of granulopoiesis masquerading as congenital leukaemia.[15] It is always of a myeloid type. In case 2 we know that the karyotype was that of Down's syndrome, but the blast cells in the blood in this case were of the lymphoid series. Although the karyotypes of the other two fetuses were not known, neither showed the physical stigmata of Down's syndrome.

Finally, leukaemoid or leucoerythroblastic reactions are so often observed in autopsies on stillborn infants and neonates that the perinatal pathologist is very familiar with that pattern of cell proliferation. In the leukaemoid reaction the infiltrate is polymorphic with a variety of immature blood cell precursors, the predominant series being myeloid. There is evidence, however, of an orderly progression from blast cells to more mature cell types. Contrary to what is said by some authors,[10] the leukaemoid reactions can show infiltration of extrahaemopoietic organs, but usually only to a minimal degree. The massive and destructive sheet like infiltration by monomorphic cells showing no maturation, as found in all these cases, is not seen, even in a florid leukaemoid reaction.

The mechanism by which fetal leukaemia could have caused these infants to die in utero is not totally clear, but the moderate degree of hydrops present in all three indicates cardiac failure. Interestingly, none of these cases showed evidence of leukaemic deposits in the skin, a common finding in neonatal leukaemia.

In none of the reported cases of congenital leukaemia has there been evidence of leukaemia subsequently developing in the mother. Two of the mothers presented here were investigated by a haematologist some weeks after delivery, but blood counts and peripheral films yielded normal results. All three mothers have remained well, one in fact becoming pregnant within a few weeks of the stillbirth. This further pregnancy was entirely normal, ending at term with the birth of a healthy baby.

In showing these three cases of congenital fetal leukaemia we wish to refute the claim that the condition does not exist. We also suggest that the rarity of the condition as a cause of stillbirth is more apparent than real, reflecting the general inadequacy of histological evaluation as part of the examination of the stillborn infant.

We are grateful to Mrs I M Watson for typing the manuscript.

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Acute lymphoblastic leukaemia under 2 years

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SUMMARY Presenting features and natural history were assessed in 48 children with acute lymphoblastic leukaemia less than 2 years of age at diagnosis. Of these, 16 were less than 1 year (group 1) and 32 were between 1 and 2 years (group 2). Results were compared with a group of 348 children between the ages of 2 and 14 years (group 3) diagnosed over the same period.

The children in group 1 presented with a higher prevalence of null cell acute lymphoblastic leukaemia, leucocyte counts $>100\times10^9/l$, and hepatosplenomegaly and had a higher central nervous system (CNS) relapse rate and shorter duration of remission than those in the other two groups. Disease free survival and overall survival in group 2 paralleled that of group 3, although children in group 2 had a significantly higher CNS relapse rate.

Neurological toxicity resulting from treatment with methotrexate and radiation was common in those under 2 years as a whole.

In conclusion, children under 1 year have a particularly poor prognosis, while those between 1 and 2 years have a prognosis similar to that in the older age group. Alternative approaches to CNS prophylaxis are needed to reduce the high prevalence of CNS disease and toxicity.

It has been recognised for some time that infants with acute lymphoblastic leukaemia, less than 2 years of age at presentation, tend to have a worse prognosis than older children.[1-3]

It has been suggested that babies presenting with acute lymphoblastic leukaemia under 1 year do particularly badly.[4-6] We have examined the outcome in a group of infants less than 2 years of age diagnosed between 1972 and 1980 at our hospital, comparing in particular the clinical features and survival of those under 1 year with those aged between 1 and 2 years. Data for children aged between 2 and 14 years, presenting over the same period, have been included in this study for comparison.

Patients and methods

Three hundred and ninety six children presented to our hospital with acute lymphoblastic leukaemia between 1972 and 1980. Forty eight were less than 2 years of age, of whom 16 were less than 1 year (group 1) and 32 between 1 and 2 years (group 2). The remainder (348) were between 2 and 14 years (group 3). There were eight boys in group 1, 17 in group 2, and 205 in group 3. The patients were treated on a number of protocols designed or being piloted for the Medical Research Council (MRC) working party on childhood leukaemia (UKALL), most of which have been reported elsewhere.[7] All comprised multiple agent induction with at least three drugs, usually prednisolone, vincristine, and L-asparaginase, and continuing multiple agent chemotherapy for two to three years. Dosage modification during induction did not occur in any patient.

Central nervous system (CNS) prophylaxis consisted of 24 Gy of cranial irradiation before 1979 and 18 Gy thereafter and regular intrathecal methotrexate until completion of radiotherapy. Cranial irradiation was given as soon as complete remission was achieved in 24 children under the age of 2 years, and it was electively deferred until 2 years in a further 18, prophylaxis being continued in the intervening period with regular intrathecal methotrexate. Deferral of radiation became the consistent policy from 1978 onwards. Four of the latter 18 infants, although electively deferred, never received radiation: three died before the age of 2 and one developed methotrexate encephalopathy. A further six children did not receive irradiation because of very early deaths or failure to achieve remission.

Various presenting features were assessed in the three age groups and the results compared. All patients were followed up for a minimum of five years. The following features were chosen, the first two having prognostic importance.[2 3 8]

(1) Height of initial white blood cell count, classified as $<20\times10^9$/l, 20–100×10^9/l, and $>100\times10^9$/l.
(2) Organ involvement. The presence of hepatomegaly, splenomegaly, lymphadenopathy, and a mediastinal mass was documented. Hepatomegaly and splenomegaly were termed 'massive' if below the umbilicus.
(3) Immunological surface markers. The leukaemia was classified into phenotypic subclasses using standard techniques and definitions previously described by Greaves *et al.*[9] Acute lymphoblastic leukaemia was thus divided into the four following types: common (ALL) (cALLA$^+$, la$^+$Tdt$^+$), T cell (T-ALL) (E-rosette$^+$la$^-$, Tdt$^+$), null cell (null-ALL) (cALLA$^-$, la$^+$ Tdt$^+$), and B cell (B-ALL) (Smlg$^+$, cALLA$^-$, la$^+$ Tdt$^-$).

Statistical methods. Statistical methods used were Fisher's exact probability test and the χ^2 test. Survival curves were compared using the log rank test.

Results

Presenting features. Presenting features in the three age groups are shown in Table 1.

(i) *White blood cell count*

The proportion of babies in Group 1 who had a white blood cell count $>100\times10^9$/l was significantly higher than in groups 2 (p=0·009) and 3 (p=<0·001). The difference between groups 2 and 3 was not significant. The number of patients who had a white blood cell count between 20 and 100×10^9/l was similar in all groups, while only a third of those in group 1 had a count $<20\times10^9$/l.

Table 1 *Presenting features in children with acute lymphoblastic leukaemia, relating to the three age groups*

Presenting feature	*Age group*		
	1 (<1 year) (n=16)	*2 (1–2 years) (n=32)*	*3 (2–14 years) (n=348)*
White blood cell count (×10⁹/l)			
<20	5	19	233
20–100	3	9	80
>100	8	4	35
Organomegaly			
Hepatomegaly	16	27	207
Splenomegaly	16	25	218
Lymphadenopathy	12	22	265
Mediastinal mass	0	2	33
Immune type			
Common	4	17	166
Null cell	5	2	14
T cell	0	1	33
B cell	0	0	7
Dubious or not tested	7	12	125

(ii) *Organ involvement*

The prevalence of hepatomegaly in groups 1 and 2 was not significantly different, but there was a much higher prevalence in these two groups compared with group 3 (p=0·001 and 0·005, respectively). None had hepatomegaly below the umbilicus. All 16 babies in group 1 had splenomegaly, of whom five had massive spleens extending below the umbilicus. Although the total prevalence was not significantly different from group 2, none of the latter group had massive splenomegaly. The prevalence of splenomegaly in group 1 was significantly higher than group 3 (p=0·002), but there was no difference between groups 2 and 3.

(iii) *Immunological markers*

Fifty six per cent of the patients tested in group 1, 10% of those tested in group 2, and 6% of those tested in group 3 had null-ALL. Although we were unable to apply statistical tests to these results in view of their incomplete nature, null-ALL seemed

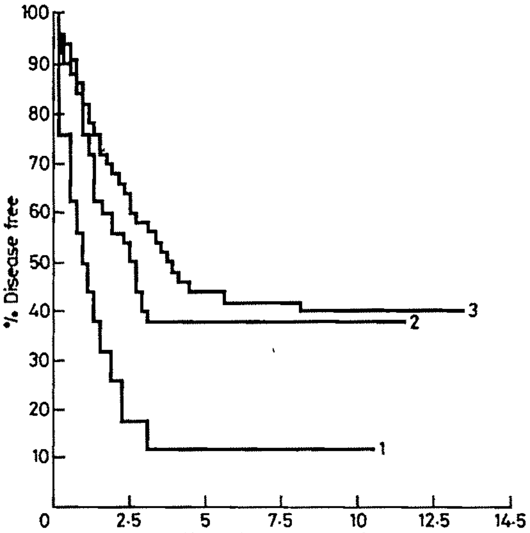

Fig. 1 *Life table showing disease free survival in the three age groups (group 1 aged <1 year, group 2 aged 1–2 years, and group 3 aged 2–14 years) of children with acute lymphoblastic leukaemia.*

to be more common in group 1 than in groups 2 and 3. Less than half of those tested in group 1 had common ALL. No child under 2 years had B-ALL, and only one had T-ALL.

Natural history.

(i) Remission induction and disease free survival
Of the 48 patients aged less than 2 years, 45 (94%) achieved remission using standard induction chemotherapy without modification of dosage. This compared with 97% of those achieving remission in group 3. Of the two patients in group 1 and one in group 2 who did not achieve remission, two died of sepsis and one of haemorrhage secondary to leucostasis.

Figure 1 shows the disease free survival in the three groups. There was a highly significant difference between groups 1 and 2 (p=0·01) and groups 1 and 3 (p=0·01) but no significant difference between groups 2 and 3. The median duration of remission in group 1 was 10 months compared with 29 months in group 2 and 41 months in group 3.

(ii) Survival
Overall survival is shown in Table 2. This was significantly higher in groups 2 and 3 than in group 1 (p=0·009). There was no significant difference in the duration of survival of children in groups 2 and 3. Two girls are still alive from group 1, both in their first remission, 42 and 116 months from diagnosis. Fourteen children (nine boys and five girls) are still alive from group 2, 12 in their first remission, between 39 and 127 months from diagnosis. No patient in group 1 and only one in group 2 with white blood cell count at diagnosis greater than 100×10^9/l has survived. Deaths in complete remission are shown in Table 2.

(iii) Relapse
Table 2 shows bone marrow and CNS relapse as first events in the three groups. The incidence of bone marrow relapse, including combined bone marrow

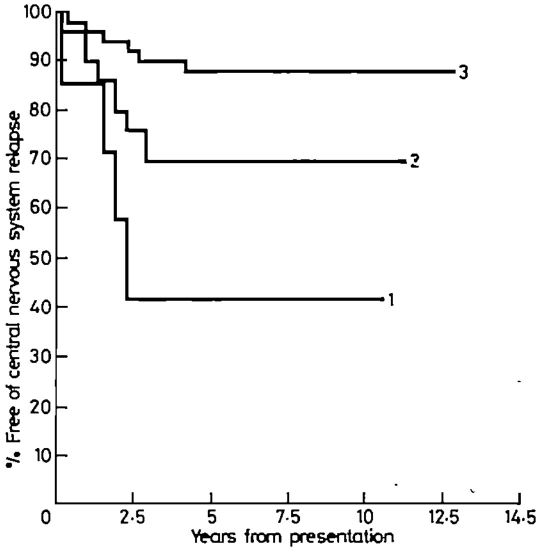

Fig. 2 *Actuarial prevalence of central nervous system relapse in the three age groups (group 1 aged <1 year, group 2 aged 1–2 years, and group 3 aged 2–14 years) of children with acute lymphoblastic leukaemia.*

Table 2 *Table of first events and survival in children with acute lymphoblastic leukaemia in the three age groups*

	Age group		
	1 (<1 year) (n=16)	*2 (1–2 years) (n=32)*	*3 (2–14 years) (n=348)*
Relapses			
Bone marrow	5	7	121
Central nervous system	4	6	27
Testis	0	0	21
Combined	2 (1 central nervous system + bone marrow + testis, 1 central nervous system + bone marrow)	1 (central nervous system + bone marrow)	4 (3 bone marrow + testis, 1 bone marrow + central nervous system)
No remission	2	1	11
Death in complete remission	1 (pneumocystis)	5 (3 septicaemia, 1 measles, 1 viral pneumonia)	15 (2 septicaemia, 7 measles, 2 cytomegalovirus, 2 encephalitis, 1 chickenpox, 1 mycoplasma)
Survival	2	14	186

and extramedullary relapses, was 44% in group 1 compared with 25% in group 2, which was significant (p=0·008). There was no difference between groups 2 and 3. Figure 2 shows that the CNS relapse rate was significantly higher in groups 1 and 2 compared with group 3 (p=<0·0001 and 0·03, respectively). Although the incidence was higher in group 1 than in group 2, this difference did not reach significance.

Table 3 shows the number of patients suffering a CNS relapse in groups 1 and 2 in relation to the time at which cranial radiotherapy was given. When CNS relapse was related to the timing of cranial irradiation in groups 1 and 2 combined, we found that of the 18 patients in whom radiotherapy was deferred to the age of 2 years, six had isolated CNS relapses and one had a combined bone marrow, CNS, and testicular relapse. Three patients, all in group 1, relapsed in the CNS before receiving radiotherapy. Of the 24 patients receiving cranial radiotherapy soon after remission, four had isolated CNS relapses and a further two had combined relapses (bone marrow and CNS). All but one were in group 2. One patient relapsed before radiotherapy. The difference in incidence of CNS relapse using these two approaches was not significant, not did it depend on the dose of radiation received.

(iv) Neurological complications

The overall incidence of major neurological complications in patients less than 2 years was 17%. Confirmed methotrexate encephalopathy occurred in four children (two in group 1 and two in group 2). Three of these had CNS leukaemia (two in group 1 and one in group 2), two of whom were treated with intrathecal methotrexate and craniospinal irradiation. Encephalopathy developed in the third in the absence of radiotherapy, which was therefore withheld. This child was 8 months of age at the time of his first CNS relapse. The remaining child who suffered encephalopathy in the absence of CNS leukaemia was 2 years old at the time of his radiotherapy. In addition, convulsions have occurred for the first time in one of the long term survivors from group 1 at 116 months from diagnosis. Computed tomography revealed calcification, which, although not diagnostic, is suggestive of methotrexate encephalopathy.

Table 3 *No of patients suffering a central nervous system relapse/total No of patients receiving radiotherapy in groups 1 and 2 in relation to timing of cranial radiotherapy*

Group	*Timing of radiotherapy*	
	*Deferred**	*Early†*
1	5/10	1/3
2	2/8	5/21

*Deferred=until 2 years of age.
†Early=on achieving remission.

Intellectual impairment occurred in three survivors. One child was severely affected, with an intelligence quotient (IQ) of 50 and is also deaf. Two of the three, including this patient, received prophylactic irradiation when less than 2 years of age.

Discussion

Most reports state that children less than 2 years old at diagnosis have a worse prognosis than those diagnosed between the ages of 2 and 10 years.[1 2] Our study seems to indicate, however, that these figures are heavily weighted by the cohort of infants less than 1 year of age, who fare particularly badly. Those aged 1–2 years seem to have survival curves very similar to those aged 2–14 years, despite the higher prevalence of CNS disease.

Babies under 1 year at diagnosis have a much higher prevalence at presentation of null cell leukaemia, white blood cell count $>100\times10^9/l$, and splenomegaly extending below the umbilicus than either those between 1 and 2 years or those between 2 and 14 years. They also have a greater prevalence of hepatomegaly than the latter group. Their disease free and overall survival is significantly less than the other two groups, and they have a much higher prevalence of CNS disease, although this only reaches significance when compared with those patients over 2 years of age. This experience parallels that of other authors,[2 5] although we did not find a high incidence of meningeal involvement at diagnosis.[5]

Early cytogenetic studies on the leukaemic clone of cells has only recently become routine at our hospital. The recent recognition of the (4:11) translocation (t4:11) in acute lymphoblastic leukaemia and its unsustained response to standard chemotherapy in young babies[10 11] makes it likely that at least some of the infants included in our study have possessed these abnormal chromosomes, which may help to account for their poor survival. It has also been shown that children with t4:11 tend to present with the same features as we have found in our group of infants. Typically, the patients are less than 1 year of age, have high white blood cell counts at diagnosis, and do not express the common acute lymphoblastic leukaemia antigen.[10] Their prognosis is poor.

Age is said to be an independent prognostic factor,[4 6] but our finding of a number of poor prognostic features in infants in the first year of life, including hepatomegaly, massive splenomegaly, and high white blood cell count,[3] [4] makes it difficult to confirm such a statement. It has recently been suggested, however, that age of less than 6 months seems to be an independent prognostic variable.[5]

CNS disease is particularly prevalent in infants aged less than 2 years at diagnosis and especially so in infants aged less than 1 year. It was initially thought that the high prevalence of meningeal involvement might be due to the practice of deferring cranial irradiation until after the second birthday. It is true that more patients in group 2 had early radiation than in group 1 and that the prevalence of CNS disease is lower in this group, but none the less the percentage of patients relapsing in group 2 despite early radiotherapy is the same as in those in whom radiation was deferred. Certainly, when these two approaches were compared statistically the prevalence of CNS relapse did not differ significantly. A similar experience is shared by Reaman *et al*, who found that there was no difference in CNS relapse rate between those in whom prophylaxis combined cranial radiation and intrathecal methotrexate and those in whom intrathecal methotrexate was used alone.[5] It has been noted in our study, however, that more patients relapsed before receiving radiotherapy in the group of children in whom it was deferred (16%) than in those who received early radiotherapy (4%). These patients were all in group 1, and it may reflect an inherent propensity for early CNS disease in the very young.

The high prevalence of neurological complications found in our series of 48 patients under 2 years is perhaps not unexpected. Several studies have revealed that although most children have IQs within the normal range after treatment with standard CNS prophylaxis and oral methotrexate, those under 3 years at the time of radiation have significantly lower IQs than those treated at an older age.[12–14] Moss *et al* also noted greater impairment in intellectual abilities in the youngest children.[15] It is not surprising therefore that intellectual impairment was found in three children, two of whom received cranial irradiation under the age of 2 years. It is for this reason that our policy since 1978 has been to defer cranial irradiation until after the second birthday, and this also warrants alternative approaches such as triple intrathecal chemotherapy to decrease CNS morbidity.[16]

Methotrexate neurotoxicity is more commonly encountered in children with previous CNS leukaemia[17] where the cumulative dose of intrathecal methotrexate is high in combination with cranial radiotherapy. As the prevalence of CNS leukaemia is high in those aged under 2 years methotrexate encephalopathy is a real cause for concern. Indeed, we found that out of 13 children aged under 2 years who developed CNS disease, three developed severe methotrexate neurotoxicity. Two further children with fits and changes in their computed tomograms compatible with toxicity did not have CNS disease.

In summary, this study confirms suspicions that infants less than 1 year at presentation have a very poor prognosis, while those between 1 and 2 years show long term survival comparable to that of older children. Whether the outlook will be improved by more intensive chemotherapy remains unclear, but in view of the high prevalence of CNS disease and toxicity, alternative approaches to CNS prophylaxis need to be found.

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1987	April 7–10
1988	April 12–16
1989	April 11–15

At University of Warwick:

1990	April 3–7
1991	April 16–20
1992	April 7–11
1993	April 19–23 (provisional)
1994	April 11–15 (provisional)

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Intensive chemotherapy for non-localised Burkitt's lymphoma

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SUMMARY Between 1982 and 1984, 24 consecutively diagnosed children from Iraq with non-localised Burkitt lymphoma (Murphy stages II, III, and IV) were eligible for treatment with a multi-drug rotating chemotherapy schedule. This schedule was intensive and included early treatment directed at the central nervous system but was of only six months' duration and fairly inexpensive compared with schedules recently advocated for use in the developed world. Some patients had 'debulking' abdominal surgery, but no radiation treatment was used. There were a number of complications related to early treatment, some of them fatal, but of 13 patients entering complete remission 12 are long term survivors who are free of disease and, hopefully, cured. These results represent a substantial improvement over our experience before 1982 (6·9% survival).

A similar treatment approach might be adopted by other centres, especially those in developing countries where cancer accounts for a rising proportion of childhood death but whose resources are limited.

Although Burkitt's lymphoma[1] is one of the most responsive tumours to chemotherapy, patients with advanced disease have proved difficult to cure.[2 3] Previous experience in Iraq is that the survival of patients with non-localised disease has been only 6·9%,[4] and other centres in developing countries, using non-intensive chemotherapy with or without radiotherapy, have reported similar results.[5–7]

The recent introduction of more intensive chemotherapy regimens has led to much improved survival for children with all categories of non-Hodgkin's lymphoma, including those B cell tumours of undifferentiated histology that represent the 'sporadic' form of Burkitt's lymphoma.[8 9] Although some authors have claimed that radiotherapy is valuable in the management of children with non-Hodgkin's lymphoma,[9 10] two randomised studies have shown no benefit when radiotherapy was delivered to sites of previous bulky tumour,[11 12] a finding that complements the clinical observation that primary site recurrence is unusual in this disease. Recurrence most commonly occurs, within six months of diagnosis, in bone marrow or the central nervous system, or both, and is then difficult to control without marrow ablative ('megatherapy') approaches.[13 14]

Typical and atypical Burkitt's lymphoma constitutes about one half of all childhood non-Hodgkin's lymphoma presenting to our centre (Al-Saleem T. Unpublished data). Because of dissatisfaction with our previous treatment results, we designed a protocol that incorporated (a) careful staging, (b) the use of 'normal dose' but intensively scheduled chemotherapy with rotating drug combinations, (c) early treatment directed at the central nervous system ('central nervous system prophylaxis') with intrathecal methotrexate and moderately high dose systemic methotrexate, (d) short total duration, and (e) no radiotherapy. Debulking surgery formed no part of the protocol but was carried out in a number of patients who were admitted to the surgical units of our hospital before referral to us. The whole protocol was designed to be suitable for use in our centre in which, for example, facilities for intravenous nutrition and serum methotrexate estimation are not available and to take into account the fact that, in Iraq, parental compliance with prolonged courses of treatment is poor.

The aims of the study were to assess the practicability and toxicity of the treatment regimen in a consecutive series of patients, to determine the complete response and survival rates, and to collect information on patterns of relapse.

Patients and methods

From February 1982 to February 1984, 24 children with non-localised Burkitt's lymphoma, consecutively admitted to the paediatric oncology unit of Medical City Hospital, were entered into the study. There were 15 boys and nine girls, and their ages ranged from 2·5 to 12 years (median 4 years). Twenty three patients had had no previous treatment, and one had recurrent disease 12 months after completing six weeks of treatment with non-intensive chemotherapy (oral cyclophosphamide and methotrexate, vincristine, and intravenous cytosine arabinoside[4]). In each case the clinical diagnosis was confirmed by histological evidence of undifferentiated lymphoma or of 'L3' morphology of blasts in bone marrow. Neither immunological surface marker testing nor Epstein-Barr virus serology was available. Children with follicular centre cell or other histological subtypes of non-Hodgkin's lymphoma were not included.

The following staging investigations were carried out: full blood count, bilateral bone marrow aspiration, cerebrospinal fluid cell count and cytospin, chest *x* ray, and intravenous urogram. In addition, six non-laparotomised patients had a computed tomogram of the abdomen performed. Staging was according to Murphy's system.[8]

All patients were given oral or intravenous (if vomiting) allopurinol 50–100 mg for at least 24 hours before starting chemotherapy and for one to four weeks thereafter: an attempt was made to alkalinise the urine, using intravenous sodium bicarbonate, during courses 1–5 and 8–9. Chemotherapy was given in 11 courses at one to three weekly intervals (Fig. 1), with special emphasis on the delivery of the first five courses as soon as possible after blood count recovery (neutrophils $>1{\cdot}0\times10^9/l$).

Courses 1, 2, 10, and 11 consisted of 'CHOP' (for details, see Fig. 1), courses 3, 4, 5, 8, and 9 of moderate dose methotrexate (combined in courses 8 and 9 with VM 26), and courses 6 and 7 of cytosine arabinoside and 6-thioguanine. In the methotrexate courses one third of the dose was given as a bolus and the remainder as a 24 hour infusion. The first dose (15 mg) of folinic acid 'rescue' was given intravenously at the end of the infusion of methotrexate and repeated every six hours (eight doses in all). Serum creatinine concentration was checked 48 hours from the start of treatment with methotrexate; if the concentration was >50% higher than just before treatment folinic acid rescue was continued for five days and the next dose of methotrexate was delayed by one week. Intrathecal methotrexate was given with courses 1–6, the dose being related to age:[15] children aged 2–4 years received 7·5 mg per dose, while older children were given 10 mg. All treatment was stopped after course 11, except in one child (case 19) who had blasts in the peripheral blood at diagnosis (L3 acute lymphoblastic leukaemia) and is on continuing ('maintenance') treatment (see Results). Radiotherapy

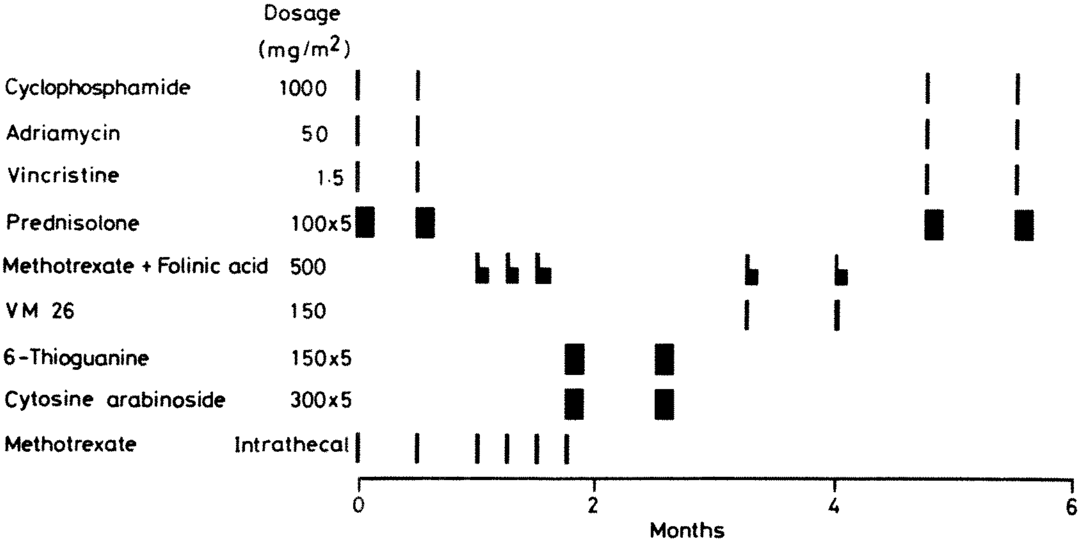

Fig 1 *Diagrammatic representation of protocol. Dosage of intrathecal methotrexate was dependent on age.*[13] *Courses 1–3 were given as close together as blood count allowed.*

was not part of the protocol but was used as 'consolidation therapy' in one patient with testicular involvement who showed an incomplete response to chemotherapy.

Before each course the patients were examined to assess tumour response and blood count, and biochemical tests of renal and liver function were performed. Bone marrow examination was carried out every eight weeks and cerebrospinal fluid cell count and cytology after each lumbar puncture. Supportive care included intravenous fluids and antibiotics, alkalinisation of urine, and blood transfusion, as necessary. Parenteral nutrition was not available.

To determine patterns of relapse, patients who completed chemotherapy had clinical examination, bilateral bone marrow aspiration, and cerebrospinal fluid study at two monthly intervals for six months and chest *x* ray and intravenous urogram at six months. After six months off treatment patients were monitored clinically.

Results

Diagnosis. All 24 patients fulfilled the clinical criteria for diagnosis of Burkitt's lymphoma, and the diagnosis was confirmed either cytologically (two cases) or histologically (22).

Staging and sites of disease. Five patients had stage II tumour, 12 stage III, and seven stage IV (Table 1). Eighteen patients had extranodal abdominal disease, 13 at multiple sites. For diagnosis, four of these children underwent biopsy examinations of other disease sites (three of the jaw and one of bone marrow). In the remaining 14, in whom disease was confined to the abdomen, laparotomy was performed. Of these 14 children, five had resection of all gross abdominal disease, but in the remainder only biopsy examination or partial resection was carried out. The incidence of involvement of the abdominal lymph nodes (five patients) was almost certainly an underestimate because laparotomies in patients with unresectable disease were not exhaustive. There were eight children with involvement of the head and neck (the jaw in seven and tonsils in one), six with involved bone marrow, and one with tumour cells in the cerebrospinal fluid. In contrast to our experience in the United Kingdom multiple simultaneous sampling of bone marrow did not, in this series, increase the yield of positive findings.

Toxicity. There was some serious toxicity related to drugs at the start of chemotherapy, with five fatalities. Two patients developed 'tumour lysis syndrome'[16] and died within 24 hours of receiving 'CHOP' course 1. Three others developed fever,

Table 1 *Staging and sites of disease in 24 patients with Burkitt's lymphoma*

Case No	*Stage*	*Site*				
		Abdomen	*Head and and neck*	*Bone marrow**	*Cerebrospinal fluid*	*Other sites*
1	II	S+N	—	—	—	—
2	III	M+N	S	—	—	—
3	III	M	—	—	—	—
4	III	M	—	—	—	Kidneys, nodes
5	II	S+N	—	—	—	—
6	IV	—	M	90	—	Liver, spleen
7	III	M	—	—	—	—
8	III	M+N	—	—	—	—
9	III	M	—	—	—	Ovaries, pouch of Douglas, kidney
10	II	—	M	—	—	—
11	III	M	—	—	—	—
12	IV	—	M	30	—	—
13	III	N*	M	—	—	—
14	III	M	—	—	—	—
15	IV	M	M	90	—	—
16	IV	M	—	90	—	Liver, spleen nodes, blood
17	IV	S	S	—	+	Spleen
18	III	M	—	—	—	—
19	IV	—	—	90	—	Blood
20	II	—	S+N	—	—	—
21	III	M	—	—	Not done	Thyroid
22	II	—	—	—	—	Testes
23	III	M	—	—	—	—
24	IV	S	—	45	—	Nodes

S=Single tumour; M=Multiple tumours; N=Regional node involvement.
*=% 'L3' blasts.

jaundice, and diarrhoea while neutropenic after 'CHOP' course 1 and, although blood cultures yielded negative results, it was assumed that sepsis was the cause of death. In the surviving patients the interval between 'CHOP' courses 1 and 2 was only 2½–3 weeks and between courses 2 and 3 was only 2 weeks. After the first 'CHOP' course, treatment was well tolerated, with close adherence to the prescribed schedule and with only seven recorded episodes of toxicity, including one of neutropenia and fever, one of severe oral ulceration with raised serum creatinine concentration after treatment with methotrexate, and one of raised serum creatinine concentration alone after treatment with methotrexate. Thus only three admissions to hospital were required after a total of 144 chemotherapy courses. No adjustments to chemotherapy dose were made during the study.

It should be emphasised that some patients were in very poor general condition (Fig. 2) and that many had recently undergone major surgical procedures. There is little doubt that these factors contributed to the early mortality and morbidity related to chemotherapy. Surprisingly, the mean duration of symptoms, before treatment, in those patients who did not achieve complete remission was the same (four weeks) as in those patients who did. A similar observation has been made in Algerian patients.[7]

Response (Table 2) and survival. Two patients died and a third was lost to follow up without receiving any chemotherapy. In the remaining 21 patients chemotherapy began within one (19 children) or two weeks (two) of diagnosis. One child was lost to follow up after course 1. Six patients succumbed to complications related to treatment, five of them after chemotherapy (see Toxicity) and one after surgery (faecal fistula with sepsis), and are grouped together as 'early deaths'. Two of these children (cases 17 and 21) died within 24 hours of starting chemotherapy, too early to assess tumour response;

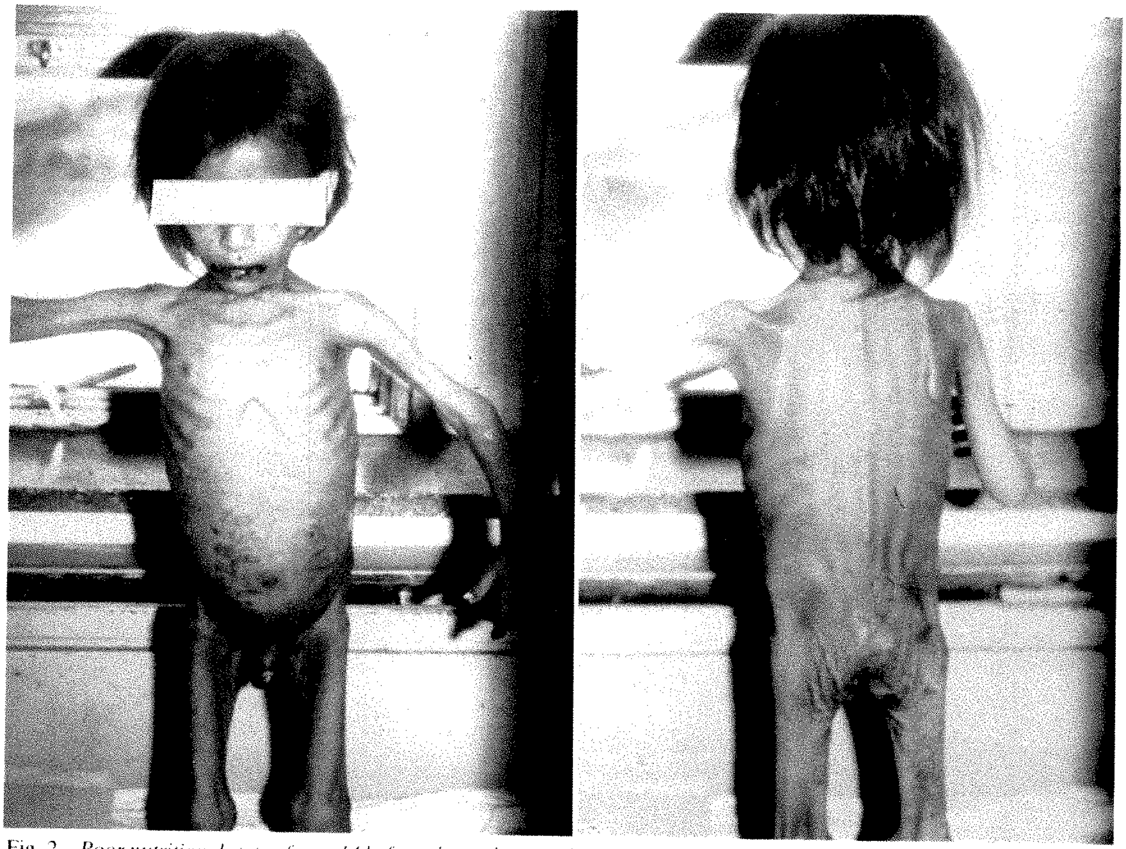

Fig. 2 *Poor nutritional state of case 14 before chemotherapy. He is a long term survivor.*

Table 2 *Summary of outcome of 24 patients with Burkitt's lymphoma. Numbers in parentheses indicate patients who did not receive chemotherapy*

State stage	*Lost to follow up*	*Early death*	*Partial response*	*Complete response*	*Total*
II	—	1	1	3	5
III	2 (1)	3 (1)	—	7	12
IV	—	4 (1)	—	3	7
Total	2	8	1	13	24

in the other four (cases 3, 7, 16, and 24) there was clear evidence of tumour regression at the time of death seven days to two months after diagnosis.

Of the 22 patients with follow up information, 13 (59%) achieved complete remission—three of five with stage II tumour, seven of 10 with stage III, and three of seven with stage IV. In all but two instances, complete remission was reached before chemotherapy course 3. At diagnosis, four children had abnormal intravenous urograms, which consisted of hydronephrosis (three cases) and nonfunctioning kidney (one); all returned to normal during treatment.

The patient (case 22) who presented only with bilateral testicular involvement and showed incomplete regression of disease (partial response) was given testicular irradiation (18 Gy). Tumour cells occurred in the bone marrow and blood at four months from diagnosis, however, and he died soon afterwards.

Lymphoma recurred in only one (case 12) of the 13 patients who achieved complete response; this stage IV patient relapsed in the central nervous system and jaw and died two months later. The 12 remaining children are still in continuous complete remission eight to over 35 months (median 21 months) after diagnosis (Fig. 3). Eleven have been off treatment for two to over 29 months (median 17 months). One child with L3 acute lymphoblastic leukaemia is on continuing ('maintenance') treatment with oral methotrexate/6-mercaptopurine and pulses of L-asparaginase, vincristine, prednisolone, and adriamycin.

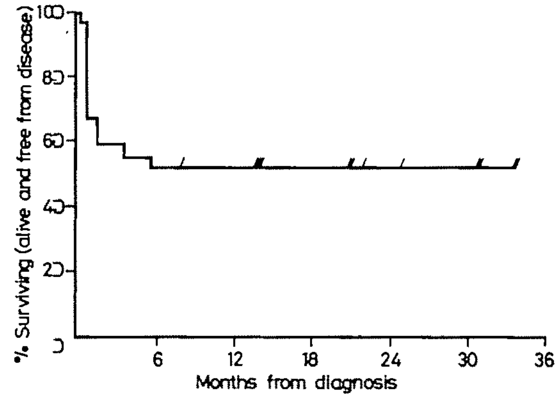

Fig. 3 *Actuarial survival curve (all patients).*

Discussion

The design of this schedule was based on a United Kingdom Children's Cancer Study Group multidrug protocol that gave unexpectedly good results (69% two year disease free survival) in patients with non-localised (stage II-IV) abdominal non-Hodgkin's lymphoma.[12] In that study the addition of radiotherapy did not improve the prognosis. In an attempt to avoid the early bone marrow and central nervous system relapse so characteristic of both endemic and non-endemic Burkitt's lymphoma, the first five courses of our protocol were administered as close together as blood counts allowed and included treatment directed at the central nervous system in the form of intrathecal and moderately high dose systemic methotrexate. Given the intensity of treatment, 'maintenance' chemotherapy was deemed unnecessary.

It has been suggested that debulking surgery reduces the relapse rate in patients with Burkitt's lymphoma,[17] and laparotomy is still advocated in some centres.[18] In our series a higher proportion (4/5) of patients who underwent initial debulking of abdominal disease survived than of those whose tumours were considered inoperable (5/11). The group who underwent debulking, however, included two patients with stage II disease, whereas all patients in the group who did not undergo debulking had stage III or IV tumours. Although numbers are small, the long term disease free survival of these five patients who did not undergo debulking suggests that surgery does not add to chemotherapy when the regimen is of sufficient intensity. This point is of particular importance in girls because the internal genitalia (ovaries, Fallopian tubes, and uterus) are often involved by tumour: had chemotherapy been used as initial treatment in patient 9 rather than surgery, castration, with its disastrous effects on the girl's later physical and psychological development, might have been avoided.

Because 11 of our patients have now been off treatment for more than six months (median 24 months from diagnosis) we hope that most of the 12 long term survivors reported here will prove to be cured. It is especially encouraging that these results, a distinct improvement over our previous experience, have been achieved after only six months of chemotherapy and without radiotherapy. The high incidence of early mortality, which parallels experience in Algeria,[7] might have been reduced by the availability of intravenous feeding, the avoidance of unnecessary surgical intervention before chemotherapy, and more careful monitoring during the post-chemotherapy 'tumour lysis syndrome'.

In a randomised study the United States Children's Cancer Study Group showed that a four drug chemotherapy programme ('COMP') was superior to a 10 drug schedule in the treatment of children with non-localised 'undifferentiated' non-Hodgkin lymphoma.[18] Patients also received high dose (30 Gy) radiotherapy, however, to sites of bulk disease. This may have compromised the delivery of subsequent chemotherapy and so explain the greater proportion of fairly late relapses in that study compared with our own. Though two year disease free survival of the 39 patients with advanced undifferentiated lymphoma (including 29 with Burkitt's lymphoma) was only 46%, Magrath *et al* considered that the addition of adriamycin to 'COMP'—that is, 'CHOMP'—may improve the outcome.[19] Sullivan and Ramirez, by contrast, reporting a median actuarial survival of 72% in children with stage II-IV Burkitt's lymphoma treated with a regimen containing very high doses of cyclophosphamide and methotrexate, recently suggested that adriamycin offered no advantage.[20]

Presentation at a late stage of disease and poor compliance with treatment are facts of life in developing countries, so we thought it appropriate to include in this analysis all patients presenting to our unit during the study, including those who received no chemotherapy at all. Though disappointing at first sight, the overall actuarial survival of 55% is encouraging in this context. Even more pleasing was the low rate of relapse (8%) among the 13 patients who achieved complete remission, suggesting that rotation of drug combinations, as in our regimen, may diminish the need for very high dose chemotherapy schedules except in patients, such as those with stage IV disease due to involvement of the central nervous system, identified as being in a very bad prognosis category. This point is of major importance for developing countries and relevant to centres in the developed world because, apart from their greater toxicity, high dose approaches require more intensive nursing and medical support than is usually available. They are also very expensive. To treat a 20 kg child, for example, the cost of methotrexate and folinic acid in the induction phase of the schedule of Sullivan and Ramirez is roughly $8250 (late 1985 prices) for these drugs in the 'maintenance' phase—a total of over $16 700.[20] The cost of methotrexate and folinic acid in the National Cancer Institute schedule is similar.[19] In our protocol, by contrast, the total cost of methotrexate and folinic acid is $950.

Nkrumah and colleagues recently reported from Ghana that 28 children with 'massive' abdominal disease had been treated with intrathecal methotrexate and, in a prospective randomised trial, with short courses either of cyclophosphamide (1400 mg/m^2) alone or intravenous cyclophosphamide (700 mg/m^2), vincristine, and low dose cytosine arabinoside.[21] That there was no difference in complete response rate and survival between the two randomised groups is of interest, but the most provocative feature of this small study is that the disease free survival (58%) of patients who received cyclophosphamide alone is similar to that of our patients, treated with a more prolonged and complex regimen. If these findings are confirmed in a second Ghanaian study now in progress (Neequaye J. Personal communication) there will be a case for a randomised trial of high dose cyclophosphamide versus a more intensive multi-drug regimen, such as ours, in sporadic Burkitt's lymphoma.

Our data indicate that many patients with advanced Burkitt's lymphoma can be cured by short but intensive chemotherapy using rotating drug combinations without radiotherapy and, in at least some cases, without major surgery. Though administered without intensive nursing support and facilities such as intravenous feeding and serum methotrexate assay, treatment was associated with little morbidity except during remission induction. We believe our results have implications for other paediatric units, especially those in other developing countries where economic factors and practical considerations have hampered progress in the treatment of advanced childhood cancer.

Added in proof

More recent follow up is now available (July 1986) on the 12 patients surviving when this paper was submitted. One (case 19) relapsed 22 months from diagnosis and died two months later, but the 11 remaining children (three stage II, seven stage III, and one stage IV) are alive, well, and in complete remission 20–44 months (median 38) from the end of treatment.

Since the completion of this study, we have treated a further 19 patients with advanced Burkitt's lymphoma using this regimen. There were two early deaths, but 17 patients entered complete remission: 16 of these children are alive, well, and free of disease at the time of writing.

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Response to bronchodilators assessed by lung mechanics

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SUMMARY Abnormalities of compliance and functional residual capacity were shown in eight young children aged 2–8 years with asthma during an acute attack. In a randomised, placebo controlled study treatment with bronchodilator (salbutamol) was associated with a significant improvement in compliance and lessening of hyperinflation as shown by a reduction in functional residual capacity.

Asthma is a common illness in young children.[1] Unfortunately, the response to treatment with bronchodilator in such patients is considered to be small and less predictable than in older children and adults.[2] Knowledge regarding the response to treatment remains limited because of the difficulties in obtaining objective measurements of lung function at this age. Previous studies that have attempted to assess the effectiveness of such treatment with bronchodilators in young children have used a modification of the forced oscillation technique for determination of resistance.[3] This technique relies on the assumption that the respiratory system functions as a single unit, which may not be valid in a disease such as asthma that can cause non-uniform, asymmetrical changes. Also as the respiratory system can be affected by such problems as upper respiratory tract infections, common in young children, it cannot be universally applied.

Despite these limitations, Groggins *et al* have been able to show changes in resistance in response to oral theophylline and salbutamol[4] and nebulised ipratropium bromide and salbutamol but not clemastine[5] in young children. The same group, however, were unable to show either reduction in resistance measured by the forced oscillation method or a fall in thoracic gas volume measured plethysmographically after treatment with nebulised salbutamol in wheezing children less than 18 months of age, and suggested this as an age limit below which treatment with bronchodilators might not be effective.[6]

Recently, we have been able to perform measurements of both functional residual capacity and compliance of the respiratory system reliably and accurately in children aged 2–7 years.[7] In a preliminary study using these tests we showed significant abnormalities in both lung volume and compliance in children with severe and symptomatic asthma. In adults similar abnormalities can be reversed by appropriate treatment to relieve airways obstruction.[8] This study investigated whether the combined techniques of measurement of compliance of the respiratory system and functional residual capacity could similarly be used in young children to document the response to treatment with bronchodilators.

Patients and methods

Study protocol. Eight children (six <5 years of age) admitted to our hospital with acute asthma were studied. The study group consisted of five boys and three girls aged 2·1 to 8·0 years, with a mean age of 4·9 years. The children were entered into the study as soon as intravenous treatment for status asthmaticus was stopped and they were able to tolerate regular treatment by nebuliser. Immediately before a scheduled inhalation of treatment with bronchodilator the child visited the respiratory laboratory. Functional residual capacity and compliance of the respiratory system were measured (see below). The child was then randomised to receive either saline (3 ml) or salbutamol (2·5 mg if <5 years of age and 5 mg if >5 years) in 3 ml of saline through a nebuliser. Ten minutes later compliance of the respiratory system and functional residual capacity were again measured. Those children who had received salbutamol returned immediately to the ward and those who had received saline were given their scheduled dose of salbutamol before leaving the laboratory. This procedure was repeated at the time of the next scheduled treatment, the child receiving the alternative solution.

Lung function measurements. All measurements were performed with the child in a sitting position breathing into a water sealed spirometer (Gould Pulmonet 3) through a face mask.

First functional residual capacity was measured by helium gas dilution. Equilibration was assumed when there had been a change of less than 20 ml in functional residual capacity over a 30 second period. Compliance of the respiratory system was then measured by weighted spirometry. After establishing a constant end expiratory level on the spirometric volume recording a 500 g brass weight was placed on the spirometer bell. This produced a constant positive pressure within the circuit of approximately 2 cm H_2O and increased the end expiratory level. Airway pressure was measured through a side port (Sanborn pressure transducer, model No 268 B). The weight was removed after a new stable baseline had been achieved, the end expiratory level then returning to the previous baseline. This procedure was repeated five times during the study. Combined compliance of the respiratory system and spirometer circuit was calculated from the mean volume and pressure changes of the five weight applications. Compliance of the spirometer circuit alone had been previously calculated by applying a series of weights to the bell with the circuit closed, this was then subtracted from the total compliance to give compliance of the respiratory system. Volumes were all corrected to body temperature, pressure, and saturation conditions.

The measurements together take less than five minutes and are reproducible (a coefficient of variation of <10% for repeated measurements both in healthy children[7] and children with asthma).

All calculations of compliance of the respiratory system and functional residual capacity were performed by one of us (AG). Individual traces were coded so that this researcher was unaware of the patient's characteristics and the relation to the trial schedule. The results are expressed as a percentage of the predicted height and weight using our own data from 60 healthy children of a similar age group.[7]

Table *Mean (range) changes in fractional residual capacity and compliance of the respiratory system in response to treatment with saline and salbutamol (expressed as percentage of predicted for height)*

	Saline		*Salbutamol*	
	Before	*After*	*Before*	*After*
Functional residual capacity	133 (111–157)	134 (119–147)	137 (124–158)	125 (111–145)
Compliance of the respiratory system	72 (51–95)	70 (47–95)	71 (49–93)	82 (56–103)

In the three older children it was possible to make peak flow measurements in addition to measurements of compliance of the respiratory system and functional residual capacity.

Ethical permission. Ethical permission for this study was granted by King's College Hospital ethical committee, and parental consent was also obtained.

Statistical analysis. Changes in functional residual capacity and compliance of the respiratory system with salbutamol and placebo were compared and assessed for significance using the paired Student's *t* test.

Results

All eight children had raised functional residual capacities and reduced compliance of the respiratory systems (Table) at the start of the study compared with our data for normal children for this age group.[7] There was no significant difference between the baseline measurements, expressed as a percentage predicted for height of our data for normal children[7] before administration of saline and salbutamol (Table). Administration of saline was

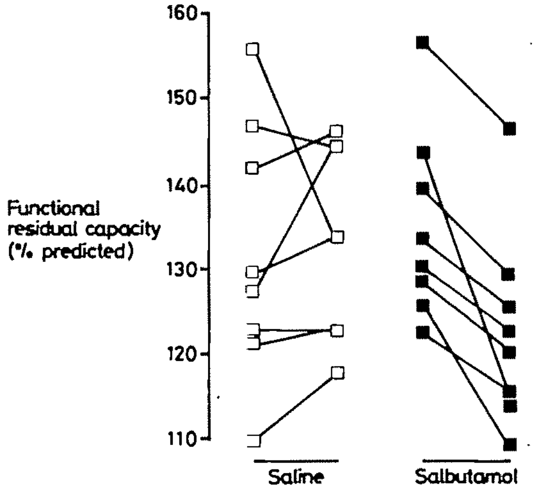

Fig. 1 *Changes in functional residual capacity in response to administration of saline and salbutamol (results expressed as a percentage of the predicted normal value for height). Individual children's responses to either saline or salbutamol are shown by linked data points.*

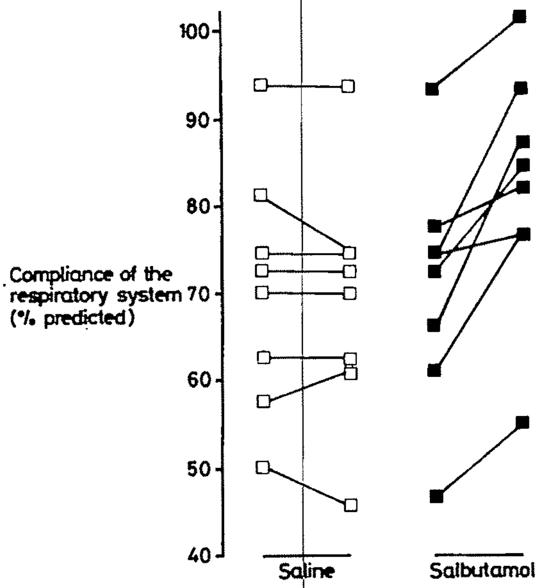

Fig. 2 *Changes in compliance of the respiratory system in response to administration of saline and salbutamol (results expressed as a percentage of the predicted normal value for height). Individual children's responses to either saline or salbutamol are shown by linked data points.*

associated with only a small variable change in both functional residual capacity (mean change 1·1%) and compliance of the respiratory system (mean change 2%). All changes are expressed as the difference between measurements before and after nebulised treatment, both measurements expressed as the percentage predicted for height using our own data for normal children.[7] Administration of salbutamol was associated with a consistent reduction in functional residual capacity, mean change 12·3% (Fig. 1), and a rise of compliance of the respiratory system, mean change 11·5% (Fig. 2) ($p<0·05$).

Only three children were able to perform peak flow measurements reproducibly. Administration of saline was associated with a small but variable response (changes of −7%, 0%, and +3%), peak flow measurements being expressed as percentage predicted for height using the data for normal children of Lunn.[9] Administration of salbutamol was associated with a consistent improvement in peak flow (changes of 15%, 13%, and 20%).

Discussion

Successful clinical management is essential to be able to diagnose accurately, describe the pattern and severity of the disease, and monitor the response to treatment. Chai *et al* assessed the value of methods of measurement commonly used in young children with asthma: clinical examination, history, pulmonary physiology, medication requirements, and school activity.[10] Their conclusion was that physiological measurements of pulmonary function were very important and provided the only objective measurement available in the assessment of state of asthma. Traditionally, peak expiratory flow has been used to assess state of asthma, particularly the response to treatment. Its main recommendation is its simplicity, which means that the test can be performed repeatedly and at home.[11] Peak expiratory flow, however, is influenced mainly by obstruction in the larger airways, thus large abnormalities of small airway flow, which occur in such children, may not be detected by peak flow measurements.[12] In young children measurements of peak flow also may be unreliable because of limited patient cooperation.

In this study the combined measurements of compliance of the respiratory system and functional residual capacity were not only well tolerated but also showed abnormalities of compliance and lung volume. Rises in lung volume in older children have previously been documented by plethysmographic measurements both in severe chronic asthma[11] and in response to antigen induced asthma.[13,14] In the present study these abnormalities of both compliance and lung volume were consistently reversed by treatment with bronchodilators but not with saline and confirm earlier reports from adults and older children. McIlroy and Marshall measured the mechanical properties of the lungs in patients with asthma at rest and during exercise and showed increased stiffness of the lungs, which was less pronounced after treatment with bronchodilators.[15] Woolcock and Read found that lung volume may be raised as much as three to five litres above normal in acute asthma attacks and that this was reduced by appropriate treatment.[16] Even among asymptomatic children (aged 8–13 years) Tooley *et al* found similar abnormalities, which again were reversed by treatment with bronchodilators.[17] They went on to emphasise the importance of early detection and treatment of this abnormality to prevent possible permanent structural changes as a result of hyperinflation.

It is suggested from these preliminary results that this technique, combined measurement of compliance of the respiratory system and functional residual capacity, may be useful in assessing response to treatment in young children with asthma in whom peak flow measurements may not be possible. Further work is necessary to assess whether the magnitude of the response is related to the age of the child or the severity of their disease.

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Slow release theophylline in preschool asthmatics

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SUMMARY A double blind crossover trial with active or placebo slow release theophylline (Slo-phyllin) in children with asthma aged up to 4 years is described. Although no difference in symptom scores was shown, other differences in favour of active treatment were noted. We conclude that this preparation is of benefit in the management of the wheezing preschool child. The value of symptom scores as an index of clinical improvement is discussed.

Theophylline can be an effective drug for less severe chronic perennial asthma in older children[1 2] and is widely prescribed for the preschool child, especially when beta_2 sympathomimetics have failed to control symptoms. It is said to be easily administered. The bronchodilator effect is related to plasma concentration.[3] Interindividual variations in plasma concentration for a given dose and intraindividual variations in concentrations during a 24 hour period are well recognised in children.[4] There is, however, little information on its use or effectiveness in the preschool child.

Assessment of outpatient anti-asthmatic treatment in the young child is difficult. Respiratory function tests, if they can be used at all, are not reliably reproducible. Recourse is made to parental opinion, often formalised by the use of a diary card for symptom scores. The aims of this study were to assess whether twice daily slow release theophylline, prescribed as closely as possible to the manufacturer's recommendations, was effective in controlling asthmatic symptoms in the preschool child and to examine the value of the symptoms score in assessing clinical improvement.

Patients and methods

Children aged up to 4 years diagnosed as having asthma were enrolled into the study, after acute admission or outpatient referral, with a wheezing illness. In each case there was a history of recurrent wheezing or coughing episodes resolving either spontaneously or with treatment. No other cause for these symptoms was found. They were given Slo-phyllin (Lipha Pharmaceuticals Ltd) or placebo in a double blind crossover study for 24 weeks. Active and placebo periods alternated at six weekly intervals, the child being allocated to the initial active or placebo treatment at random. Throughout the study a beta_2 sympathomimetic was prescribed to be taken when necessary for symptoms of cough or wheeze. Additional treatment—for example, steroids—was at the discretion of the general practitioner or admitting hospital doctor.

Parents scored symptoms of cough, wheeze, daytime activity and night time symptoms daily on a 4 point ordinal scale where a maximum score of 3 was obtained for maximal symptoms. Use of additional medication and comments were also recorded. No run in period was used. The scores from the last five weeks of each six week period were studied, however, to avoid a carry over effect. The effectiveness of the treatment was judged by change in symptom scores, use of additional medication, number of hospital admissions for acute attacks of asthma, and parental preference.

Statistical analysis was by paired *t* test and Wilcoxon signed rank test for non-parametric data.

Results

Twenty nine children were entered into the study; six were lost to follow up, three refused to take the drug, and four were non-compliant as judged by negligible theophylline concentrations in the active treatment period. The records of the 16 remaining children were studied. Mean age at entry was 2·6 years (range 10 months to 4 years). Fourteen had a family history of atopy and nine had had eczema. Mean age at onset of symptoms was 1·1 years (range <1 to 36 months) and frequency of symptoms varied from several times weekly (eight) to weekly (three) or less than once weekly (five). Ten had had previous admissions to hospital for asthma.

Mean (SD) theophylline dose was 10·3 (2·0) mg/kg/dose (range 7·6–14·3 mg/kg/dose); mean

Table 1 *Comparison of symptom scores in active and placebo treatment periods in children up to 4 years of age with asthma*

Score	*Treatment*		*Mean difference*	*95% Confidence interval*	*p Value**
	Active (mean (SD))	*Placebo (mean (SD))*			
Total	57·8 (55·1)	55·3 (53·4)	−2·6	−24·6, 29·7	0·73
Daytime	42·8 (40·9)	41·4 (39·8)	−1·4	−18·8, 21·6	0·74
Night time	15·0 (15·1)	13·8 (14·9)	−1·2	−6·3, 8·7	0·75

*Wilcoxon signed rank test.

plasma concentration of theophylline measured three to five hours postdose was 9·1 (2·1) mg/l (range 6·4–13·2 mg/l). Side effects, consisting of mild gastrointestinal symptoms, were seen in two patients and settled on reduced dosage. Behavioural and sleep disturbances were not noted.

No difference in symptom scores was found between active and placebo treatment periods for either total daily scores or for separate scores for daytime and night time symptoms (Table 1). There were similar numbers of consultations of general practitioners, days when bronchodilators were used, and prescriptions issued for steroids or antibiotics during the active and placebo periods (Table 2).

One child was admitted to hospital during the active treatment period, but five children were admitted during the placebo period (four once and one twice).

Table 2 *Comparison between active and placebo treatment periods in children up to 4 years of age with asthma*

	Treatment	
	Active	*Placebo*
General practitioner consultations	10	14
Additional use of bronchodilators (patient days)	240	223
Courses of steroids prescribed	2	3
Courses of antibiotics prescribed by general practitioners	9	9
Admission to hospital with asthma	1	6
Parental opinion of period in which child was better controlled	8	0

Parental opinion sought before the randomisation code had been broken was that their child had been better controlled during the active treatment period in eight cases. In the remaining eight there was no preference. No parent thought that the placebo treatment was superior. When the symptom scores were classified according to parental preference, however, there was a significant improvement in scores in the active treatment period in those children whose parents preferred the active treatment and a significant deterioration in symptom scores in the active treatment period in those whose parents had no preference (Table 3).

There was a reduction in symptom scores between the first and second active or placebo treatment periods, which was independent of order of randomisation.

Discussion

We have shown no significant alteration in symptom scores in children of up to 4 years with asthma who received Slo-phyllin at a dose close to the maximum recommended by the manufacturers (it is our experience that children are usually prescribed considerably less than this by general practitioners).

It is probable, none the less, that the drug as currently recommended is of benefit in relieving asthmatic symptoms in children under 4 years of age. There were fewer admissions to hospital of children taking the active treatment; of the six children admitted because of mild attacks of asthma, five were taking placebo, one of whom was admitted

Table 3 *Comparison of symptom scores in active and placebo treatment periods with reference to parental preference. No parent preferred the placebo period*

Score	*Parents prefer active treatment*		*Parents have no preference*	
	Mean difference in symptom score	*p Value*	*Mean difference in symptom score*	*p Value*
Total	21·2	0·03	−26·3	0·02
Daytime	14·6	0·06	−17·4	0·02
Night time	6·6	0·01	−8·6	0·04

twice. While 50% of parents thought that their child was better when taking the active treatment, none thought that placebo was superior. These observations indicate a clinically important improvement with active treatment.

In those subjects whose parents thought their child was improved during the active treatment period there was a significant decrease in symptom scores during this period. The children recognised by their parents as benefiting from active treatment tended to be those with lower overall scores, suggesting that children with milder asthma benefited most from this form of treatment, as has been suggested previously.[5]

Although the blood concentrations of theophylline achieved were within the range thought to be effective,[3] others have recommended that concentrations of 10–20 mg/l should be maintained.[2] It is possible that larger or more frequent doses than are currently recommended by the manufacturers would be more effective for the preschool child, who is known to eliminate the drug more rapidly, but close monitoring of blood concentrations would be necessary.

Although Slo-phyllin is said to be easy to give, the beaded capsule contents being simply disguised in food, seven out of 23 (30%) of the children in this study did not or would not take the prescribed drug. Others have reported similar problems.[5] The observed trend towards an improvement in symptoms with time indicates that any child on regular prophylaxis should have regular critical review of the need for such treatment.

This study has highlighted some of the problems of using the symptom score as an index of severity of asthma. Parentally derived symptom scores have a wide numerical range, because of the wide variation in observers. The power of this study to detect a fairly small change in score—for example, 15%—is low. A study population of 800 would have been needed to show a change of this size with 80% power at $p=0\cdot05$. Although a distinct preference for the active treatment was shown by parents, and this was borne out by a significant improvement in symptom scores in the group whose parents preferred the active treatment, there was an equally significant change in symptom scores in the opposite direction in the group whose parents showed no preference—yet they should, all other factors being equal, have preferred the period of treatment with placebo. By asking parents to complete a diary for symptom scoring they are probably made to concentrate on some of the important symptoms, but parental preference is probably determined by additional unidentified factors that must have a stronger influence.

It therefore remains possible that benefit from active treatment in other children was not recognised because of deficiencies in the symptom score as a tool in clinical assessment. There are several other reasons why this may be so. Decisions as to the efficacy of treatment rely on impressions of dyspnoea and severity of wheeze. Even the older sufferer may not perceive important airways obstruction, and there is no means of identifying the poor perceiver except by objective tests of lung function.[6] Paediatric practice is further hindered by the perceiver being at one remove from the sufferer. Intrinsic to the symptom score is a total reliance on subjective parental responses. While many parents may be sensitive to the level of their child's respiratory difficulty, others are known both to underestimate its severity, with possibly the eventual production of permanent chest deformity, and to over react to mild attacks when objective assessment shows little or no evidence of lower airways obstruction.[7]

The optimum method of assessment of preschool children with asthma has yet to be established.

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Erythromycin versus tetracycline for treatment of Mediterranean spotted fever

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SUMMARY Eighty one children aged between 1 and 13 years participated in a randomised comparative trial of tetracycline hydrochloride and erythromycin stearate for treatment of Mediterranean spotted fever. Both therapeutic regimens proved effective, but in patients treated with tetracycline both clinical symptoms and fever disappeared significantly more quickly. Likewise, when those patients who began treatment within the first 72 hours of illness are considered the febrile period had a significantly shorter duration in the group treated with tetracycline. One patient was switched to tetracycline because there was no improvement of clinical manifestations, with persistence of fever, myalgias, and prostration, after receiving eight days of treatment with erythromycin. These results suggest that tetracyclines are superior to erythromycin in the treatment of Mediterranean spotted fever.

Mediterranean spotted fever is an acute infectious disease caused by *Rickettsia conorii.* During the last few years there has been a resurgence of this disease in Mediterranean countries.[1] Likewise, acquired sporadic cases have recently been reported in northern Europe[2 3] and the United States.[4] Treatment with tetracyclines or chloramphenicol is effective, but tetracyclines can cause undesirable side effects, especially in children under the age of 8 years, and with chloramphenicol there is a risk of bone marrow toxicity.

Some cell culture studies have shown that erythromycin is an effective in vitro agent against various species of rickettsieae.[5 6] We undertook a randomised clinical trial comparing tetracycline hydrochloride with erythromycin stearate to see if erythromycin could constitute a useful and less toxic therapeutic alternative in children with Mediterranean spotted fever.

Patients and methods

We included in the study all children diagnosed as having Mediterranean spotted fever and admitted during 1983 and 1984 to the Hospital de Sant Llàtzer, Terrassa, and Clínica Infantil del Nen Jesús, Sabadell (Spain). Eight patients, who in the week preceding the study had received antibiotics, were not included in the trial; neither were those with a history of allergy to tetracyclines and erythromycin.

The diagnostic criteria of Mediterranean spotted fever were as follows: presence of typical clinical manifestations plus tache noire and/or a positive serologic result by means of indirect immunofluorescence against *R. conorii* (a fourfold increase in the titre of acute serum over convalescent serum or a titre over 1:40 in those few cases in whom only one test was possible).

Eighty one children fulfilled the conditions for inclusion in the study; 12 who did not were excluded. Patients were treated at random with either erythromycin stearate or tetracycline hydrochloride according to a set of computer generated aleatory numbers. Over a period of 10 days patients received daily doses of either erythromycin 50 mg/kg (12·5 mg/kg four times a day) or tetracycline 40 mg/kg (10 mg/kg four times a day). Temperature was taken at least every six hours by nursing personnel not related to the study, and symptoms were evaluated daily until disappearance.

On admission the following laboratory studies were carried out: haemogram, erythrocyte sedimentation rate, urea, creatinine, total bilirubin, and electrolyte concentrations, serum glutamic pyruvic transanimase, serum glutamic oxaloacetic transanimase, alkaline phosphatase, creatine kinase, and lactate dehydrogenase activities, prothrombin time, total protein and protein electrophoresis, urinalysis, Weil-Felix reaction, indirect immunofluorescence against *R. conorii*, and blood cultures. Electrocardiograms and chest *x* ray films were also obtained. At the end of three weeks a clinical revision and new serological, haematological, and biochemical determinations were made. Apyrexia was defined as a temperature of less than 37°C taken in the armpit. Student's *t* test was used for statistical analysis.

Results

Of the 81 patients studied, 50 were boys and 31 girls. Ages ranged between 1 and 13 years. Thirty four patients received tetracycline hydrochloride and 46 erythromycin. One patient began treatment with erythromycin but was later switched to tetracycline. This 7 year old boy presented with fever, headache, and myalgias of 24 hours' duration. On physical examination a tache noire was noticed on the scalp accompanied by enlarged lymph nodes and maculopapular rash affecting the palms of the hands and the soles of the feet. There was no improvement of clinical manifestations, with persistence of high fever (39–40°C), headache, myalgias, and prostration on the eighth day of treatment with erythromycin. After two days of treatment with tetracycline fever subsided and clinical symptoms markedly improved. As the patient had not completed the prescribed 10 day course of antibiotic regimen this case was not evaluated in the results, and we think that this must be considered as an example of erythromycin proving ineffective.

Mean (SD) ages of the patients were similar in both groups (6·9 (2·2) years in the group treated with tetracycline *v* 5·9 (2·6) years in the group treated with erythromycin). Maximal temperatures recorded on admission were also similar (39·6 (0·6)°C *v* 39·5 (0·7)°C, respectively). The interval between first occurrence of symptoms and beginning of treatment was somewhat longer in the group treated with tetracycline (4·3 (1·8) days) than in the group treated with erythromycin (3·5 (1·7) days); this difference was significant (p<0·05).

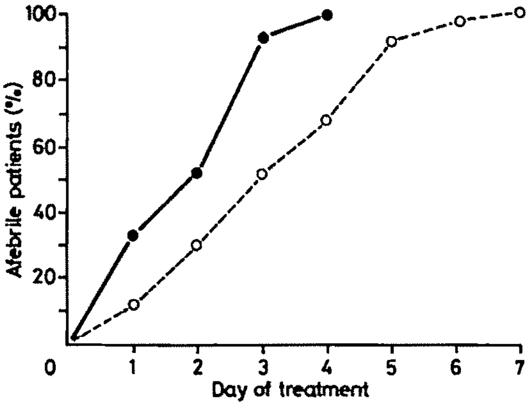

Figure *Accumulated percentage of afebrile patients on successive days after the beginning of treatment with tetracycline hydrochloride (solid line) or erythromycin stearate (broken line).*

Table *Results of a therapeutic trial, tetracycline* v *erythromycin, in children with Mediterranean spotted fever. Values are mean (SD)*

	Treatment group		*p Value*
	Tetracycline	*Erythromycin*	
n=	34	46	
Apyrexia after treatment (days)	2·2 (1·0)	3·5 (1·5)	<0·0005
Disappearance of symptoms (days)	2·4 (1·0)	3·4 (1·4)	<0·0005
Duration of febrile period (days)	6·5 (2·1)	7·0 (1·6)	NS

All patients recovered uneventfully. After the beginning of treatment fever and clinical symptoms disappeared significantly more quickly in the group treated with tetracycline (Table). Also the total duration of fever in this group was shorter, although the difference was not significant. When only the 38 patients who began treatment within the first three days of illness were considered the total duration of fever was significantly shorter (p<0·01) in the 14 patients treated with tetracycline (5·0 (0·8) days) than in the 24 patients treated with erythromycin (6·3 (1·7) days). The Figure shows the accumulated percentage of afebrile patients in each group on successive days after the beginning of treatment. No relapses were observed. One patient had side effects (diarrhoea), which may be attributed to erythromycin, but in this single case suspension of the trial was not necessary.

Discussion

Mediterranean spotted fever is a benign disease,[7 8] fatalities from which are rare (mortality of 0–2%).[9 10] On the other hand, clinical manifestations are usually severe, with intense malaise. The natural duration of Mediterranean spotted fever is from 10 to 15 days.[11] Treatment with tetracyclines or chloramphenicol shortens this symptomatic period and avoids possible serious complications. The risk of bone marrow toxicity is an argument against the use of chloramphenicol in such a generally benign disease. Untoward effects of the tetracyclines in children aged under 8 include staining of the teeth, temporary retardation of bone growth, and hypoplastic enamel.[12] For this reason the use of tetracycline antibiotics in children has been restricted, except in some diseases, such as rickettsiosis, brucellosis, and psittacosis.[13] In fact, staining of the teeth is related to the accumulative doses administered during childhood.[14] Thus it is more important to suspend the use of tetracyclines in daily paediatric practice than to avoid administration of a single course of the drug.

This study shows that tetracycline hydrochloride is superior to erythromycin stearate in the treatment of Mediterranean spotted fever. Symptoms and fever disappeared significantly more rapidly in the group treated with tetracycline. Although the difference in the total duration of fever between the two groups was not significant, this is probably due to the fact that treatment was started more promptly in the group treated with erythromycin. In fact, when only those patients who began treatment within the first three days of illness are considered the total duration of the febrile period was significantly shorter in the group treated with tetracycline. Differences in the clinical point of view between patients on tetracycline and patients on erythromycin, however, were less apparent (delay of apyrexia of about 1·5 days), except in one case of unsuccessful treatment with erythromycin.

In conclusion, erythromycin could constitute an acceptable therapeutic alternative to tetracycline for children aged under 8 years with Mediterranean spotted fever, except those with severe symptoms or serious illness.

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Renal response to arginine vasopressin in premature infants with late hyponatraemia

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SUMMARY To assess the influence of late hyponatraemia on the renal responsiveness to endogenous arginine vasopressin (AVP), urinary excretion and plasma concentration of sodium, plasma and urine osmolality, free water clearance, and urinary AVP concentration and excretion were measured in 11 healthy premature infants with a mean birth weight of 1360 g and mean gestational age of 31 weeks. Studies were performed on days 1, 5, and 19.

The development of late hyponatraemia was associated with a pronounced decline in urine osmolality, whereas urine flow rate and free water clearance increased significantly. Mean (SEM) urine AVP concentration and excretion also rose significantly from 2·15 (0·31) pg/ml and 0·36 (0·55) pg/min/m^2 on the first day to 6·5 (0·96) pg/ml and 3·85 (0·63) pg/min/m^2 on the 19th day, respectively.

When renal response to AVP was compared at different ages the highest urine osmolality and steepest response curve was observed on the first day. With development of hyponatraemia the renal response became blunted.

It is concluded that the limited tubular sodium transport and hyponatraemia hinders the establishment of intrarenal osmotic gradient, impairs renal response to AVP, and prevents excessive water retention and further fall of plasma sodium.

In a recent study on the role of arginine vasopressin (AVP) in development of late hyponatraemia in premature infants we showed a steady rise in urinary AVP excretion with age in spite of the pronounced decline in plasma sodium concentration and osmolality.[1] This finding was interpreted as indicating that the protracted volume contraction due to renal salt wasting stimulates AVP release, which, in turn, enhances free water reabsorption and contributes towards restoring the volume of body fluid compartments to normal. Interestingly, however, the rising AVP excretion was not associated with the expected rise in urine osmolality; what is more, the lowest mean value for urine osmolality was observed in the third week when hyponatraemia was already established.

On the basis of these observations it could be assumed that contrary to the general view[2] either no postnatal increase in renal responsiveness to endogenous AVP occurs over the age period studied or the renal response to AVP is blunted by late hyponatraemia.

In the present study we attempted to determine whether the impaired renal sodium conservation and hyponatraemia might limit the ability of the kidneys of premature infants to concentrate urine independent of AVP.

Patients and methods

Eleven healthy male premature infants with a mean birth weight of 1360 g (range 1020–1620 g) and mean gestational age of 31 weeks (range 29–33 weeks) were studied. All infants were delivered vaginally after uncomplicated pregnancy and labour. There were no pathological events known to increase AVP secretion during the perinatal period—that is, perinatal asphyxia, cardiopulmonary distress, or perinatal infection. They were nursed in a thermally controlled environment and fed pooled human milk. On the first day 5% glucose infusion was also given to provide daily fluid intake of 70–80 ml/kg.

Urinary excretion and plasma concentration of sodium, plasma and urine osmolality, endogenous

Table *Postnatal values (mean (SEM)) of plasma sodium concentration and osmolality, urine osmolality and flow rate, arginine vasopressin (AVP) concentration and excretion in urine, free water clearance, and fractional sodium excretion in 11 healthy premature infants*

Age (days)	*Plasma sodium (mmol/l)*	*Osmolality (mOsm/kg H_2O)*		*Urine flow rate (ml/min/1·73 m^2)*	*Free water clearance (ml/min/1·73 m^2)*	*Fractional sodium excretion (%)*	*Urine AVP*	
		Plasma	*Urine*				*Concentration (pg/ml)*	*Excretion (pg/min/m^2)*
1	138·0 (2·5)	288·0 (1·6)	159·0 (16·2)	0·26 (0·02)	0·10 (0·03)	1·79 (0·27)	2·15 (0·31)	0·36 (0·05)
5	139·6 (1·8)	290·0 (4·0)	146·0 (14·7)	0·57 (0·05)*	0·27 (0·06)*	2·02 (0·41)	4·70 (0·57)*	1·80 (0·25)*
19	130·8 (1·4)**	281·0 (1·6)*	93·0 (11·5)*	0·98 (0·09)**	0·72 (0·14)**	0·51 (0·09)**	6·50 (0·96)*	3·85 (0·63)**

*$p<0·05$ v day 1.
**$p<0·01$ v day 1.

creatinine clearance, and urinary AVP excretion were measured on the first, fifth, and 19th days of life.

Plasma and urine sodium concentrations were determined by flame photometry. Osmolality was measured by freezing point depression, using a Knauer osmometer.[3] Creatinine concentration was determined according to the method of Jaffe with some modification.[4] Urinary AVP was measured by radioimmunoassay as described by Sramkova *et al*.[5]

Informed parental consent and approval of a local ethics committee was obtained for blood sampling and urine collection.

Statistical analysis was by the unpaired Student's *t* test and log-linear correlation.

Results

Postnatal changes in plasma sodium and osmolality, urine volume, urine osmolality, free water clearance, fractional sodium excretion, and urinary excretion and concentration of AVP are summarised in the Table. There was a significant decrease of plasma sodium ($p<0·05$) and plasma osmolality ($p<0·05$) by the 19th day.

The development of late hyponatraemia was associated with a pronounced decline in urine osmolality, whereas urine flow rate and free water clearance increased significantly over this period. In spite of the falling plasma sodium and osmolality, mean (SEM) urine AVP concentration and excretion rose steadily from 2·15 (0·31) pg/ml and 0·36 (0·05) pg/min/m^2, respectively, on the first day to 6·5 (0·96) pg/ml and 3·85 (0·63) pg/min/m^2, respectively, on 19th day ($p<0·01$).

The postnatal alterations in renal concentrating performance were assessed by comparing the AVP response curves at different ages (Figure). The highest urine osmolality and steepest curve were observed on the first day. With advancing age and development of late hyponatraemia, the renal response became paradoxically blunted as indicated by the lower urine osmolality and the less steep slope of the response curve.

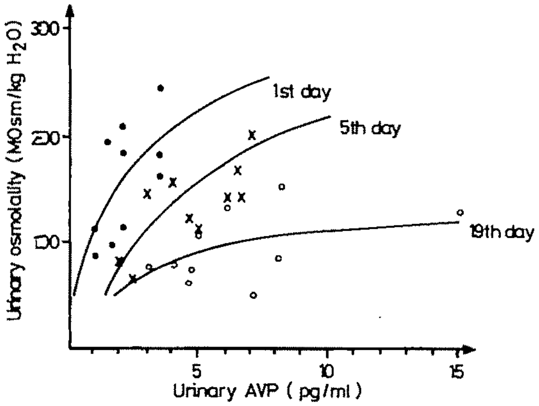

Figure *Renal osmotic response to endogenous arginine vasopressin (AVP) in premature infants on the first (●), fifth (X), and 19th (○) days of life.*

For first day, $y=112·95+70·01$, $r=0·65$, $p<0·01$.
For fifth day, $y=12·31+91·62$, $r=0·84$, $p<0·01$.
For 19th day, $y=27·99+36·71$, $r=0·45$, $p<0·05$.

Discussion

The results of the present study on renal responsiveness to endogenous AVP suggest that renal salt wasting and development of late hyponatraemia interferes with the postnatal maturation of renal concentrating mechanisms.

It has been postulated that an interstitial osmotic gradient from renal cortex to papilla should be generated and maintained for elaboration of concentrated urine.[6] [7] The generation of a hypertonic renal interstitium involves several factors, including passive medullary urea recycling[8] and active sodium chloride transport in the ascending limb of Henle's loop.[9]

Moore *et al* have shown that the fetal lamb could establish a steep intrarenal osmolar gradient already at mid-gestation and infusion of hypertonic urea induced a significant increase in intrarenal urea concentration from cortex to papilla, whereas after hypertonic administration of sodium chloride the corticopapillary sodium gradient remained unaltered.[10] These experimental data are consistent with the clinical observations of Edelmann *et al*, showing that in preterm and full term neonates the concentrating performance can be enhanced by providing high protein diet or urea supplement, but sodium chloride supplementation proved to be inefficient.[11] These findings lend support to the concept that urea as a urinary solute is of prime importance in the renal concentrating mechanism.

In newborn rats urea accounts for only 25% of papillary solute and the adult value of about 50% is only reached by 21 days.[12] In agreement with these observations Zink and Horster found that in the early distal tubular fluid of 12–15 day old rats sodium chloride comprised most of the solute but that its relative contribution to the total solute concentration markedly decreased with age.[13] It can be assumed, therefore, that in the early period of life sodium chloride plays a major role in the build up of corticopapillary osmotic gradient, whereby the intact renal tubular sodium transport is an important prerequisite of efficient renal concentration.

Rees *et al* recently showed that urine osmolality response to AVP was more pronounced in premature infants with hypertonic dehydration than in those recovering from hyponatraemia.[14] This observation has been thought to indicate that in hypernatraemia the delivery of glomerular filtrate high in sodium and the medullary hypertonicity are important factors in enhancing renal response to AVP. With this suggestion in mind it is reasonable to speculate that hyponatraemia, the lower rate of sodium delivery to the distal nephron, and the subsequent decrease of renal solute gradient may limit the production of concentrated urine.

In addition to the diminished renal osmotic gradient, the increased renal prostaglandin production may also be considered as a factor contributing to the impaired renal response to AVP. In a group of healthy premature infants a progressive increase in urinary prostaglandin E excretion has been shown during the first three weeks of life when hyponatraemia and decreased renal responsiveness to AVP developed.[15]

In conclusion, our findings indicate that renal salt loss and volume stimulated increased AVP secretion may both be involved in the development of late hyponatraemia of prematurity. On the other hand, the limited renal tubular sodium reabsorption and the hyponatraemic state may hinder the establishment of intrarenal osmotic gradient and impairs renal response to AVP, thus preventing excessive water retention and further worsening of hyponatraemia.

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Short reports

Computerised biofeedback achieving continence in high anal atresia

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SUMMARY Computerised biofeedback has been used to attempt to improve continence in three boys with high anal atresia. The results obtained so far have been extremely encouraging. Over a period of six months progressive improvement has taken place and been maintained in each child.

Anal atresia is a congenital abnormality in which the rectum fails to reach the anus. High (supralevator) anomalies have an increased incidence in boys. The rectum usually reaches the upper surface of the pelvic floor, but the anal canal is absent and the levator floor is well developed but does not descend further than the bowel. Part of the external sphincter is invariably present but is insufficient to have any useful function. The condition is diagnosed at birth and managed surgically; initially a colostomy to relieve the obstruction may be needed and a pull through procedure performed at 6–12 months.[1] Subsequent to this, sphincter response to rectal distension is usually lost and the continence mechanism disturbed. Secondary surgical procedures endeavouring to improve continence include:[2]

(1) Imitating external sphincter function using skeletal muscle with or without a muscle stimulator.
(2) Strengthening the musculus puborectalis by free muscle transplantation.
(3) Mimicking the action of the internal sphincter using smooth muscle transplantation.
(4) Levator anal release creating an independent muscle sling.

In most cases bowel training regimens based on psychological training, medication, and dietary manipulation are used. These children are often incontinent for many years before achieving control with the help of any of the above methods.[3] Failure may bring about the performance of a permanent colostomy in adolescence. Biofeedback techniques using a simple pneumatic device have been used for this condition,[4] and other operant conditioning regimens have also been used to increase faecal continence.[5]

Patients and methods

Three boys aged 6–9 years with corrected high anal atresias are already being treated.

An electromyograph is connected to the child by geltrode self adhesive pads and relays electrical signals produced by muscular activity. The signals are conveyed to a computer by connecting leads and a junction box that matches the signal to the computer's needs and protects the child against any shock hazard. The computer is a BBC Model B and provides audiovisual feedback. A disk system stores the program. Muscle activity, as a function of time, is traced on the screen at an adjustable predetermined speed. Increasing muscle activity is indicated by a rising trace and decreasing activity by a falling trace.[6] Each program can be fully adjusted instantly to the requirements and capabilities of the child. Some programs used are as follows.

Shape. The target pattern is made up of two horizontal parallel lines. The child endeavours to keep the trace above the lines by contraction of his pelvic floor musculature. This is performed on each visit and a printed report kept of the child's performance. Although we are aware that differences in exact location of sensors and skin condition between sessions means this is not a reliable comparison, it is a useful tool for encouraging the child and his family as an improvement in his performance, as measured by the trace, occurs.

Engines. Images of train engines are drawn on the screen. Appropriate muscle contraction is rewarded by an auditory signal 'toot-toot' as the trace hits an engine.

Tennis. A man moves up and down the left hand of the screen serving balls that are returned if hit by a bat controlled by the child. Contracting muscles

Table *Details of the three cases with high anal atresia before and after computerised biofeedback*

Case No	*Age (years)*	*No of treatments*	*Continence*		*Staining of anus*		*Rectal sensation*	
			Before	*After*	*Before*	*After*	*Before*	*After*
1	6	11	No control. Frequent major accidents	Occasional accidents. No continence aids at weekends	Always stained	Occasional staining	No sensation of oncoming stool	Always aware of sensation of oncoming stool
2	9	9	No control. Frequent major accidents	Occasional small accidents. Only wearing continence aids for school	Always heavily stained	Occasional staining	No sensation of oncoming stool	Usually aware of sensation of oncoming stool
3	7	11	No control. Frequent major accidents	Occasional small accidents. Only wearing continence aids for games	Always stained	Often stained	No sensation of oncoming stool	Usually aware of sensation of oncoming stool

moves the bat upwards and relaxing muscles downwards.

Monkey. A mechanical toy may be switched on and off by the computer switching as a result of muscle contraction.

On his first visit the child is shown how the computer works, using sensors on the forearm muscles to show that it is painless and can be fun. Terms that each child understands are used. He is then assessed as to the amount of voluntary activity around his perineum and also the extent to which he simultaneously uses other muscle groups. He is then placed in a position that counteracts these additional movements. Two sensors are placed as close as possible laterally to the anus. The muscles are susceptible to fatigue so the child is treated for short periods once weekly, the active phase of treatment being about 10 minutes. Encouragement is given for practice at home.

Results

In conjunction with psychological methods and a multidisciplinary approach this technique has achieved a high level of success. Initially, the children were referred with excoriation of their perineums, which were difficult to keep clean, and had poor motivation to be continent. Treatment has resulted in healthy perineums, and the children are now motivated to do well, both competitively with the computer games and at home between treatments (Table). As the internal sphincter is mainly concerned with prevention of soiling this is likely always to be present, but these children can now successfully pass a stool, having sensed its presence, in the lavatory, and are no longer wearing continence aids all of the time. The parents are extremely pleased with the success of the treatment so far.

Discussion

This method involves teaching awareness of the pelvic floor, strengthening muscular responses, and teaching when to contract the muscles. The children enjoy their treatment and remain enthusiastic. The anatomy of normal continence is disturbed, but we believe that our treatment will speed up the usual continence acquiring process in this group of children.

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Changing demography of trisomy 18

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SUMMARY The incidence of trisomy 18 in Leicestershire during the years 1980–85 inclusive was one in 3086 births. Eleven of the 21 babies born with trisomy 18 in this period were delivered by caesarean section. Median and mean periods of survival were 2·5 and 22 days, respectively.

Parents who have had a child with a serious and life threatening disorder such as trisomy 18 (Edwards' syndrome) often seek information concerning its local demography and likely prognosis. Experience of trisomy 18 in Leicestershire over the last six years suggests that this disorder is more common than generally recognised and that the pattern of survival is changing.

Patients and methods

Data for the years 1980–85 inclusive concerning all cases of trisomy 18 delivered in Leicestershire plus those terminated after diagnosis at amniocentesis were obtained from the records of (1) the Leicestershire perinatal mortality survey, (2) all local neonatal units, (3) the clinical genetics service, and (4) the cytogenetics units in Leicester, Nottingham, and Sheffield. The maternal and paediatric records of all cases were obtained and family visits were conducted after approval by the local ethical committee to obtain full details of family pedigrees.

Results

Incidence. Twenty three cases were ascertained (nine male and 14 female), of which two were terminated after diagnosis at amniocentesis. When these two cases are included the incidence during the study (total births 70 985) is one in 3086 births.

Obstetric data. Hydramnios was noted during the third trimester in 11 of the 21 pregnancies. Mean gestation at delivery was 36·7 weeks. Eleven of the 21 babies were delivered by caesarean section, electively in four cases because of intrauterine growth retardation and poor placental function and

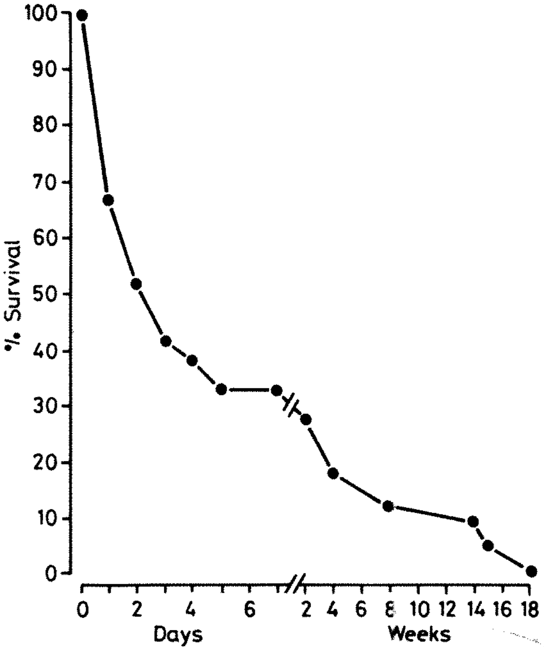

Figure *Survival of study cases by life table method.*

by emergency in the remaining seven because of fetal distress during labour.

Clinical and genetic data. Mean weight, length, and head circumference at birth were 1580 g, 41·9 cm, and 30·4 cm, respectively. Mean (SD) parental ages at birth were 30·02 (7·63) years for fathers (mean paternal age for all births in England and Wales in 1982=29·63 years; t=0·245, p=0·5) and 28·56 years for mothers (mean maternal age for all births in England and Wales in 1982=26·37 years; t=1·32, p=0·1). Six mothers were aged over 35 years at the time of delivery.

In each case the diagnosis was suspected at or shortly after birth and was confirmed as full trisomy 18 by conventional G banded karyotype. Median and mean survival were 2·5 and 22 days, respectively. The range of survival was from 45 minutes to 18 weeks. One third of the babies died within 24 hours, and two thirds died within the first five days (Figure). Necropsy was performed in nine cases, revealing congenital cardiac abnormality in eight and tracheo-oesophageal fistula with oesophageal atresia in four.

Discussion

This retrospective survey of trisomy 18 yielded three unexpected observations.

Firstly, the incidence of 1 in 3086 births was higher than that noted in surveys of comparable size. An early study of the incidence of trisomy 18 found three cases in a consecutive series of 10 345 births occurring in a hospital in Wisconsin, giving an incidence of roughly 1 in 3500.[1] Larger surveys have suggested lower incidence figures of around 1 in 5000 to 1 in 7000 births.[2 3] We have no explanation for the higher incidence noted in Leicestershire, which showed no clear temporal, geographical, or social class clustering.

Secondly, the incidence of delivery by caesarean section, which was performed in 11 of the 21 cases, was high. This confirms a previous report[4] and illustrates the potential value of developing a safe means for rapid fetal karyotyping during the third trimester for cases in which a severe fetal abnormality is suspected because of intrauterine growth retardation or hydramnios, or both.

Finally, the data derived in this study indicate that the pattern of survival in trisomy 18 is changing. It was noted 20 years ago that over 80% of trisomy 18 babies survived for at least two weeks, with 50% surviving for at least two months.[5] A more recent study of cases born during the years 1972–82 in Queensland yielded median and mean life expectancies of five and 48 days respectively,[3] compared with values of 2·5 and 22 days obtained in this study. This tendency towards shorter survival may be explained by changing patterns of patient management associated with early diagnosis. For those involved in counselling parents of a neonate with trisomy 18 it is important to remember that survival into childhood and beyond has been noted on rare occasions.[6]

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Implantable subcutaneous venous catheters

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SUMMARY Twelve totally implantable subcutaneous central venous catheter systems were used in paediatric oncology patients. Complications were few—namely, blockage and four infective episodes, all of which were successfully treated. Infective rate was 0·189 episodes per 100 days' use, which is substantially lower than that reported with other central venous catheters.

The problems of long term venous access in patients, particularly children, who are receiving prolonged or intensive chemotherapy are well known. Tunnelled central venous catheters were introduced in an attempt to circumvent these problems.[1, 2] Such catheters are liable to be colonised by skin microorganisms, such as coagulase negative staphylococci, and can result in serious infection, especially in immunocompromised patients.[3]

For the last year a totally implantable subcutaneous central venous catheter and portal with a self sealing septum for hypodermic needle entry (Port-a-Cath) has been employed in managing children with malignant disease. We have analysed our experience, particularly in relation to the number of infective episodes, patient acceptability, and complications necessitating removal.

Materials and method

The system. The Port-a-Cath system (Pharmacia) consists of a silastic catheter, which is inserted usually through the subclavian vein into the superior vena cava. The catheter is connected distally to a metal reservoir, which has a self sealing septum on the top (Figure). The whole system was implanted subcutaneously under general anaesthesia by one of two surgeons. Access to the system is a sterile procedure, using a Huber point needle, which is pushed through the subcutaneously placed self sealing septum. The system can be used from the day of insertion and was in several of our patients. Maintenance of the system consists of monthly heparinisation, which was carried out by ward staff certified to give intravenous treatment. Before use, the system was flushed with Hepsal (Hepsal, Wedde Pharmaceuticals Ltd), any blood samples that were required were obtained, and then reflushed before connecting to a continuous infusion. The system was used for sampling, to administer chemotherapy, continuously or by bolus, and for delivery of blood or blood products.

Complications. Complications related to the maintenance and use of the systems were recorded both by unit staff and by parents. All febrile episodes, defined as a temperature reading ≥38°C, were investigated by blood cultures both from the catheter and a peripheral site. Infections related to the catheter were defined as febrile episodes when micro-organisms were recovered from the catheter or when pus was obtained from the site of insertion of the Port-a-Cath.

Results

During the study 12 children had a system inserted. Their ages ranged from 1 to 6 years (median 1½ and mean 2½ years), and they were being treated for acute leukaemia (five cases), neuroblastoma (three), embryonic sarcoma (two), aplastic anaemia (one), and chronic haemolytic anaemia (one). The indications for implanting the system were all children treated in the Oncology Unit at Alder Hey Children's Hospital under 4 years of age who were to receive prolonged chemotherapy; or older children who required frequent venous access whose home circumstances or behaviour favoured a sealed subcutaneous system. There was only one such older child in our study.

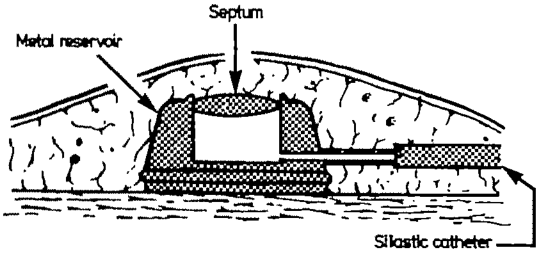

Figure *The Port-a-Cath system, showing the inserted silastic catheter connected distally to the metal reservoir, which has a self sealing septum on top.*

To date, catheters have been in situ for a total of 75·75 patient months, ranging from one to 14 months (mean 6·3 months). Each system was in regular use until treatment was completed. Complications have been few. One child developed hypofibrinogenaemia at the time of insertion and subsequently a haemothorax, which required drainage. This was considered to be secondary to her tumour and chemotherapy, rather than due to insertion of the catheter. Blockage in the system was the problem most commonly encountered, occurring in 10% of infusions, but this was always resolved by flushing or changing the Huber needle. Total blockage requiring removal of the system has not been experienced.

Eighteen febrile episodes occurred during the study, 13 when patients were neutropenic. In four of the episodes micro-organisms were isolated from the catheter and in three of these also from peripheral blood. On three occasions coagulase negative staphylococci were isolated and on one *Candida albicans*. All were successfully treated with appropriate antibiotics. A focus of infection not related to the catheter was found in five other febrile episodes, and the remainder were apparently noninfective. This represents an infection rate of 0·189 episodes per 100 days of catheter use.

Only one system required removal during use. This child had coagulase negative staphylococcal bacteraemia that was treated successfully. The system required flushing and replacement of the needle on several occasions and was compounded by the need for prolonged and repeated access at the same skin point of entry. Wound sepsis developed over the reservoir with a purulent exudate. On exploration of the chest wall site the reservoir was found to be surrounded by a pool of sterile pus and the system was removed. The line was cultured but was sterile. No other children had wound breakdown, malposition, or breakages.

Discussion

The use of tunnelled central venous catheters as an effective and safe way of giving prolonged chemotherapy and supportive care in paediatric patients has been advocated.[4] Such lines, however, are not without their problems.

A recent survey from Bristol described experiences with 49 Broviac or Hickman indwelling central venous catheters inserted in 36 children.[5] These patients were comparable with ours in terms of age, group of diseases being treated, and chemotherapy used. Twenty nine episodes of infection were encountered and on 21 occasions the catheter was removed for non-elective reasons, each catheter having an average life of 2·9 months. This represents an infection rate of 0·68 episodes per 100 days of catheter use.

The Port-a-Cath system has been developed to circumvent this problem and has been shown to achieve this successfully in our study. The infective episodes were significantly less ($p<0{\cdot}02$) compared with that reported by Darbyshire and colleagues[5] and the necessity to remove systems an uncommon event. Patient acceptability was excellent, discomfort of the wound site only occurring in one patient after insertion, and this settled after three days. Parents were pleased with the cosmetic results. Maintenance of the system is less often required than Broviac or Hickman lines, although the ideal frequency for all systems has not been determined. Two patients in the study had had Broviac catheters inserted already (two and one, respectively), two of which had been pulled out by the patients and the third of which had become infected, reflecting our general difficulties with Broviac and Hickman lines in this very young age group. We, therefore, routinely insert Port-a-Cath systems in young children less than 4 years who require prolonged venous access.

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'Near miss' sudden infant death and obstructive apnoea

K P DUNNE, M MCKAY, AND T G MATTHEWS

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SUMMARY A 4 month old girl presented with a 'near miss' sudden infant death episode for which no cause was found. Obstructive sleep apnoea syndrome subsquently developed. All symptoms ceased after adenoidectomy at age 9 months.

'Near miss' sudden infant death syndrome (SIDS) is a diagnosis based on a history of a child found apparently lifeless and requiring vigorous resuscitation to revive him. Investigations fail to reveal a convincing cause. Obstructive sleep apnoea syndrome in children and adults is rarely diagnosed in the United Kingdom compared with the experience of the United States.[1] We report a case of 'near miss' SIDS who subsequently developed obstructive sleep apnoea syndrome.

Case report

A 4 month old girl was admitted for evaluation after an unexplained apnoeic episode (lasting 15–20 seconds) at age 11 weeks. While awake, she suddenly became apnoeic and stiff, and the mother thought she was about to die. There was no history of difficulty in breathing or struggling. She was resuscitated by vigorous back slapping and was normal in a few minutes. There had been no previous episodes and her breathing was otherwise normal. She was the third child, a full term normal delivery with birth weight 3300 g and length 50 cm, after an uneventful pregnancy. There were no neonatal problems. Both the child's mother and grandfather had had tonsillectomy and adenoidectomy as children and the grandfather still snores. There was no family history of SIDS.

Clinical examination yielded normal results, except that weight (5·28 kg) and length (58·1 cm) were both less than 10th centile. All investigations (full blood count, electrolyte and calcium concentrations, electrocardiogram, and electroencephalogram) yielded completely normal results. Overnight cardiorespiratory monitoring (512 Neonatal monitor, Corometrics Medical Systems Inc) showed occasional periodic breathing but no prolonged episodes of apnoea (>15 seconds) or bradycardia (<90 beats/minute). End tidal carbon dioxide in quiet sleep was 5·0 kPa and her end tidal carbon dioxide on breathing 12% carbon dioxide could be raised to 7·5 kPa before arousal from sleep. She was diagnosed as a case of 'near miss' SIDS and received no treatment but was kept under regular outpatient review.

There were no further attacks, but from age 6 months her mother became increasingly concerned with the child's breathing when asleep. She had intermittent snoring and, despite no medical background, the mother gave a clear history of episodes of complete upper airway obstruction. The child would go quiet, the chest would move up and down, but no air was going in 'as if some one was pinching her nose'. Typically, the infant then started to cry, took a few deep gasping breaths, and woke up. This occurred two to three times a night initially, becoming almost continuous when she was seen in the outpatients ward at 8 months, causing total disruption of sleep for mother and child. There was no history of sweating with these episodes.

Examination revealed a normal child (weight 7·25 kg (<10th centile), height 64·0 cm (<3rd centile)) with no signs of right ventricular hypertrophy and no evidence of upper airways obstruction when awake. Investigations included a normal electrocardiogram and chest *x* ray film, but a lateral neck *x* ray film showed adenoidal hypertrophy. Cardiorespiratory monitoring was not repeated. After discussion with the parents laryngoscopy and bronchoscopy were performed under anaesthesia, proceeding to adenoidectomy when this confirmed pronounced adenoidal hypertrophy. Since the operation she has had no 'near miss' episodes and her breathing is normal. At age 1 year her height is now 73·3 cm and weight 8·80 kg (both 10th to 25th centile) and physical examination and development is completely normal.

Discussion

Obstructive sleep apnoea syndrome remains an uncommon diagnosis in medical practice in the UK. The pathophysiology of the syndrome is not certain, but floppy laryngeal walls combined with narrowing of the nasopharyngeal airway—for example, by adenoidal enlargement—may predispose to upper airway collapse.[1] Chronic obstruction may cause apnoea, hypercapnoea, and hypoxia. Cor pulmonale, neurological deficits, learning difficulty, failure to thrive,[2] and short stature[3] may result. Adenoidectomy results in a 'catch up' of weight and height[2 3] as in our patient. The fact that questions about sleep or sleep problems are not as yet part of the routine medical questioning may partly explain this clinical 'blind spot'. Even though all cases are symptomatic, however, there is often considerable delay in referral.[2] Clinical examination when awake may yield completely normal results, and it is important to assess the child when asleep.

The association between 'near miss' SIDS and the subsequent development of obstructive sleep apnoea syndrome is a rare one, and to our knowledge there are only 12 reported cases (including one child who died of SIDS), all published in the US.[4–6] The connection is unclear, but Guilleminault postulates that a small posterior airway at the level of the tongue may predispose to apnoea and this may be familial.[6] In our case there was no history or clinical evidence of airway obstruction in the initial 'near miss' episode. The initial polygraphic recording was normal but does not reliably exclude airway obstruction in the absence of data relating to nasal air flow. The association is, however, important. Obstructive sleep apnoea syndrome must be excluded as a treatable cause of 'near miss' SIDS. A thorough history, examination of the child when asleep, and a lateral neck *x* ray film are essential as well as cardiorespiratory monitoring. It must be noted, however, that a negative lateral neck *x* ray does not exclude adenoidal hypertrophy.[2] An otorhinolaryngological examination is mandatory if obstructive sleep apnoea is suspected on history.

Obstructive sleep apnoea is one possible cause for the failure to gain weight sometimes noted before deaths through SIDS. Guilleminault noted four siblings had died from SIDS in the five families described with a small posterior airway.[6] Such an association is speculative and obviously does not explain most cases of SIDS. Physicians must be aware, however, that children with 'near miss' SIDS may subsequently develop obstructive sleep apnoea and that this can occur at an early age. Further follow up studies may show that this association is more common than had been previously thought.

We thank Mr Collins (Consultant Ears, Nose, and Throat Surgeon) and Miss Audrey Dixon. Dr K Dunne is funded jointly by the Friends of the Rotunda and the Irish Sudden Infant Death Association.

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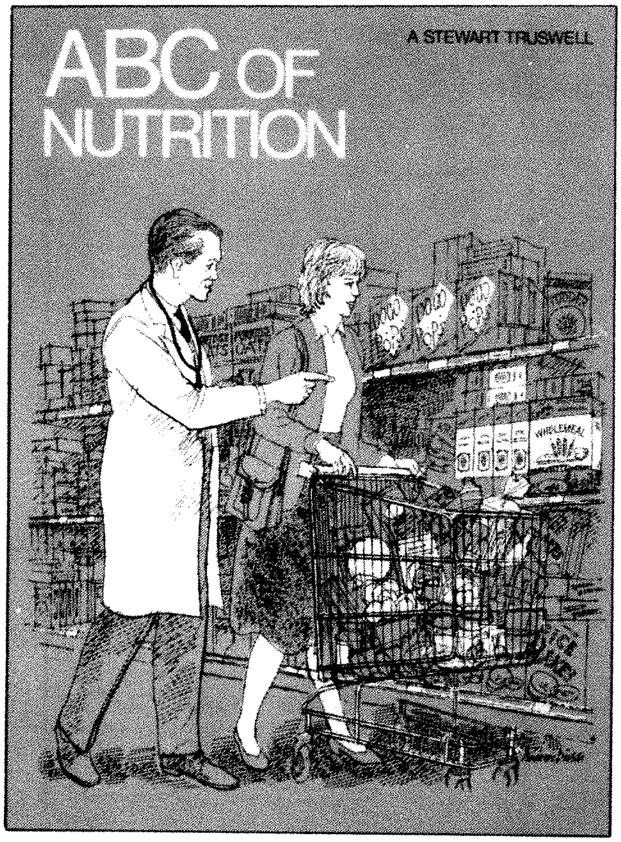

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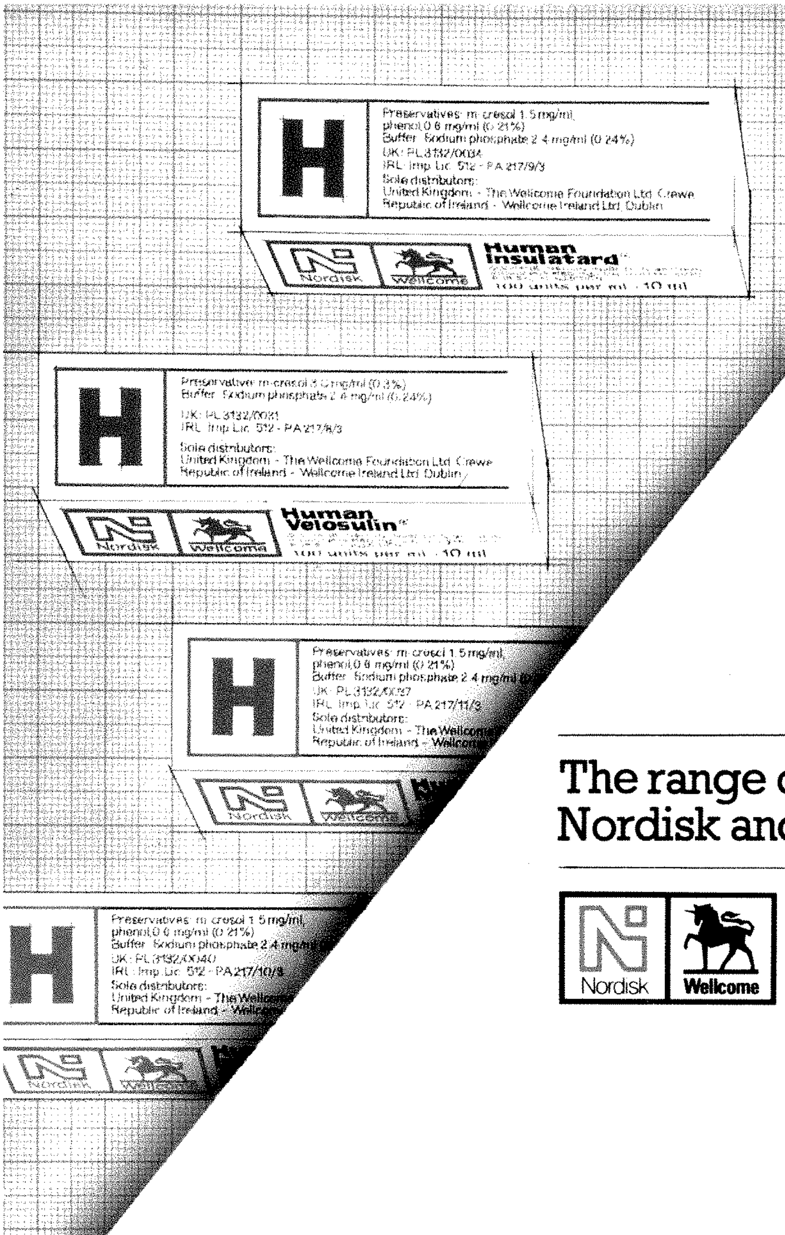
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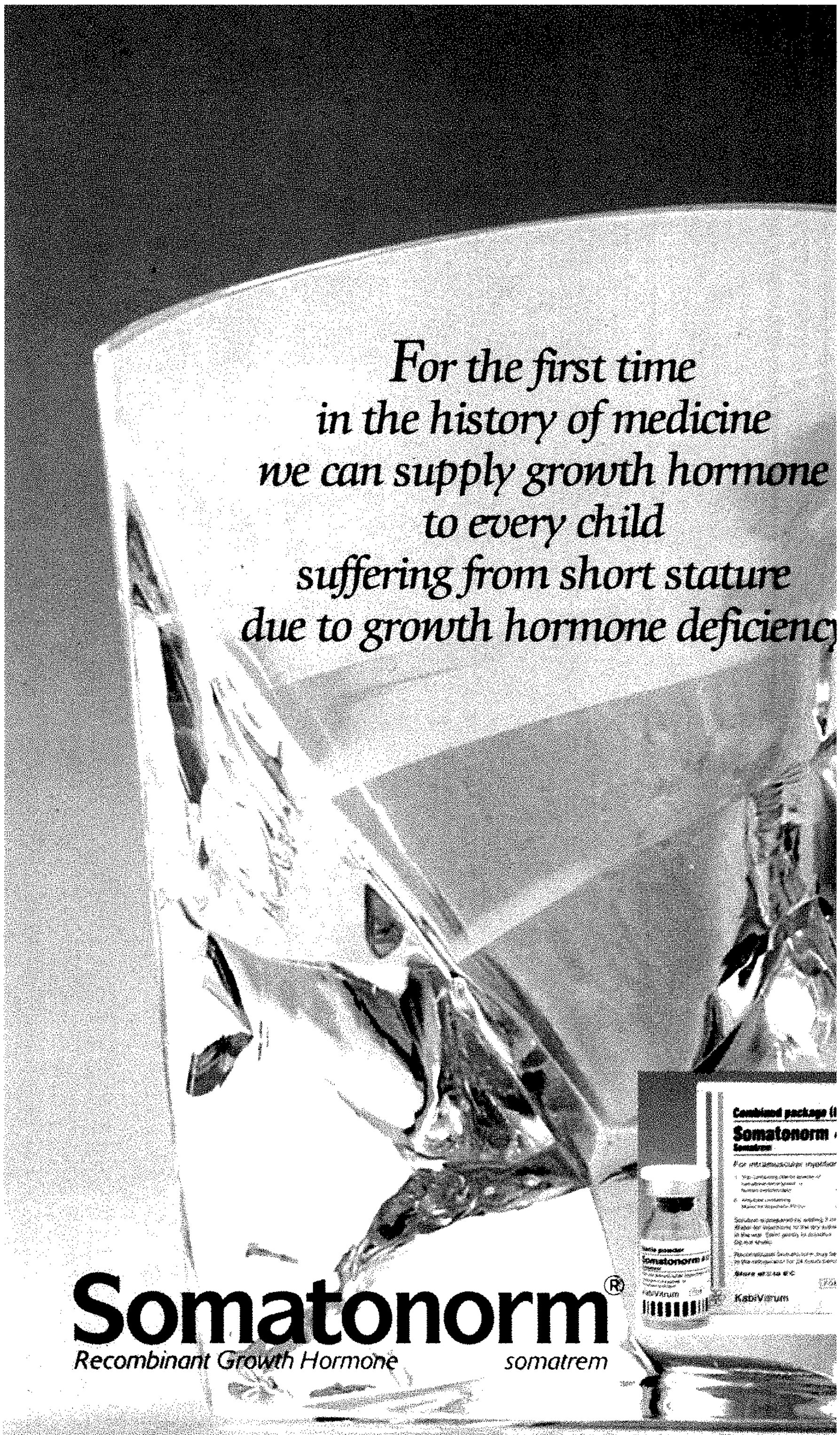
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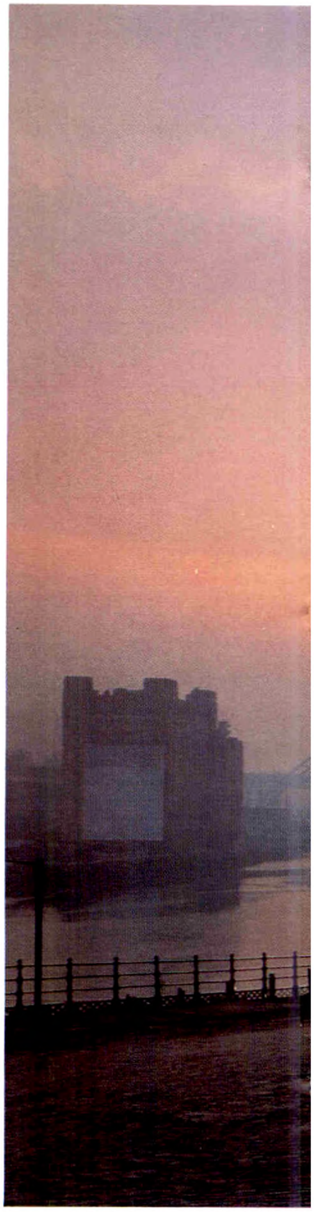

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ood. Epilim may be given twice daily
nteric coated tablets should be
wallowed whole. **Monotherapy** *Adults:*
tart at 600mg/daily increasing by 200mg
t 3 day intervals until control is achieved.
Maximum dose 2,500mg per day).
hildren over 20kg: Initially 400mg/day
ith spaced increases until control is
chieved. (Usually within the range
0-30mg/kg body weight per day).
hildren under 20kg: 20mg/kg of body
eight per day; in severe cases may be
ıcreased up to 40mg/kg day. Increases
bove this only if plasma valproic acid
evels, clinical chemistry and haematological
arameters can be monitored. **Combined**
herapy It may be necessary to raise the dose
hen used with anticonvulsants which induce
ver enzyme activity. Dosage of barbiturates
hould be reduced if sedation is observed.
)ptimum dosage is mainly determined by
eizure control and routine measurement of
lasma levels is unnecessary. **Contra-**
ıdications, Warnings; Contra-indication:
ctive liver disease. **Side effects:** Liver
ysfunction including hepatic failure resulting
ı fatalities has occurred in patients whose
eatment included valproic acid or sodium
alproate. The incidents mainly occurred during
ıe first 6 months of therapy. Clinical symptoms are
ıore helpful than laboratory investigations
ı the early stages of hepatic failure. The
nset of an acute illness, especially
ithin the first 6 months, which may
ıclude symptoms of vomiting,
ethargy or weakness, drowsiness,
norexia, jaundice or loss of seizure
ontrol is an indication for immediate
ithdrawal of the drug. Evidence to
ate does not establish which
ıvestigation could predict this possible
dverse effect: measurement of liver
ınction should be performed in the
rst 6 months of therapy in those who
eem most at risk. Hyperammonaemia
ithout hepatic damage can occur; it is
sually transient, but may occasionally
resent clinically. If so Epilim should be
iscontinued. Valproic acid inhibits platelet
ggregation. Thrombocytopenia has been
eported. Spontaneous bruising or bleeding
; an indication for withdrawal of medication.
ancreatitis, tremor, weight gain, transient
air loss, increased alertness, aggressiveness,
yperactivity, amenorrhoea, stupor and oedema
ave been reported. **Drug Interactions** Epilim
ıay potentiate monoamine oxidase inhibitors and
ther anti-depressants. Loss of efficacy of oral
ontraceptive agents does not appear to be a
roblem. **Women of Childbearing Age** Valproic
cid and sodium valproate, like certain other anti-
onvulsants, have been shown to be teratogenic in
nimals. In women of childbearing age the benefits
f these compounds should be weighed against the
ossible hazard suggested by these findings and their
regnancies should be carefully monitored. **Product Licence**
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Archives of Disease in Childhood, 1986, **61,** 1041–1043

Annotations

The sweat test

A request to the biochemistry laboratory for a 'sweat test' usually implies the measurement of the sweat sodium and chloride concentration or osmolality to support or refute the diagnosis of cystic fibrosis.

The increased concentration of electrolytes in the sweat of patients with cystic fibrosis was first described by Sant'Agnese *et al.*[1] The routine estimation of sweat electrolytes became a practical proposition after the introduction of the pilocarpine iontophoresis method for stimulating the production of sufficient sweat for reliable electrolyte estimations.[2] Previous methods of sweat collection—enclosing the limb in a plastic bag, overnight collections onto weighed pads, and even heating the whole patient—were less satisfactory and the last potentially dangerous.

The sweat test is a most valuable and relatively specific investigation to support the diagnosis of cystic fibrosis. Unfortunately, the test is performed badly at times and erroneous results, usually false high values of sweat sodium and chloride, have resulted in appreciable overdiagnosis. If false positive results are accepted uncritically by the clinician investigating a patient whose symptoms and signs suggest the diagnosis it is possible that cystic fibrosis will be incorrectly diagnosed. There is now considerable evidence that such mistakes are not rare.[3] There are many other patients who are eventually correctly diagnosed only after serious difficulties have occurred in arriving at the diagnosis; not least of the problems has been the reliability of the sweat test.

There are two important aspects to a sweat test. The first is the collection of an adequate weight of the patient's sweat to permit accurate analysis of the electrolyte content. The second is the correct interpretation of a reliable estimation of the sweat electrolyte concentrations in the light of the patient's age, clinical findings, and additional investigations.

Sweat collection

Collection of an adequate weight of sweat is usually facilitated by the prior iontophoresis of pilocarpine into a small area of forearm skin. Sweat is collected from this pretreated area onto a weighed pad applied below a waterproof covering. This classical method of Gibson and Cooke is still used in most laboratories.[2] The weight of the pad and thus the sweat is known and the electrolyte content and concentration can be estimated. Volumes over 50 mg are necessary for accurate estimations, and ideally 100 mg should be obtained.

The technical details are of paramount importance and the test has the potential for numerous errors. There may be contamination of the skin, instruments, or collecting apparatus or evaporation of the sweat from the pad from inadequate seals. Problems with dilution of the sweat specimen should be avoided by adequate laboratory quality control.

An alternative method of collection of sweat from stimulated skin uses the Macroduct, which is a concave plastic disc with a central small aperture leading to a spirally configured transparent fine plastic tube; the sweat can be observed travelling along the tube as it collects.[4 5]

An alternative to collecting sweat is to estimate the chloride content of the sweat in situ using a chloride sensitive electrode.[6] In practice this method is not recommended and, in our experience of patients referred to our unit, is associated with frequent errors when used by routine laboratories.

There is no place for semi-quantitative screening tests: if cystic fibrosis is suspected a formal sweat test should be performed.

Thus adequate sweat collection involves obtaining at least 50 mg, preferably 100 mg, of the patient's sweat, avoiding contamination, evaporation, or dilution errors, permitting an accurate estimation of the true sweat electrolyte concentration.

Interpretation of sweat electrolyte values

The interpretation of the sweat electrolyte results is usually straightforward; virtually all mistakes result from the incorrect determination of the concentration of sweat electrolytes.

There is excellent separation of the sweat electrolyte concentrations of patients with cystic fibrosis and unaffected individuals;[7] although obligate heterozygotes have intermediate values, the differences are not sufficient to allow their identification in the general population. In cystic fibrosis the sweat sodium and chloride values are above 60 mmol/l, with a mean of around 100 mmol/l, whereas in unaffected individuals the mean is around 30 mmol/l. Five to 10% of normal adolescents and adults, however, have values greater than 60 mmol/l—that is, in the lower cystic fibrosis range; furthermore, an occasional patient will have sweat electrolytes within the normal range.[8]

Sweat electrolyte values above the normal range, between 60 and 80 mmol/l, usually cause the practical difficulties. The usual response of the clinician and biochemist to such raised values is to repeat the test on a number of occasions. In some patients the first raised values will be revealed as an obvious laboratory error and subsequent values will fall well within the normal range. In many individuals—usually older children and adolescents—there will be genuine sweat electrolyte values, however, of over 60 mmol/l—that is, definitely outside the accepted normal range and within the lower range of values for patients with cystic fibrosis. Such results require careful evaluation, for the repeated sweat tests have usually caused considerable anxiety for the patient and parents.

Other conditions in which there are high concentrations of sweat electrolytes should be considered, but they are rarely the cause of the abnormal result—for example, adrenal insufficiency, glucose-6-phosphate deficiency, nephrogenic diabetes insipidus, hypothyroidism, mucopolysaccharidosis, malnutrition, anorexia nervosa, fucosidosis, ectodermal dysplasia, glycogen storage disease type I, nephrosis, Mauriac syndrome, familial cholestasis, and familial hypoparathyroidism.[9]

The relation of the sodium to the chloride value is helpful, for if a marginal result is from a normal individual the sodium is usually higher than the chloride value. Furthermore, the sum of the sodium and chloride values usually lies below 140 mmol/l. In patients with cystic fibrosis with the marginal results the chloride is usually higher than the sodium and the sum of sodium and chloride values is usually greater than 140 mmol/l.[10] Our own data would support the value of these simple yet valuable observations.[11]

Further evaluation of marginally raised sweat electrolyte concentrations involves repeating the sweat test after giving oral 9α-fludrocortisone, 3 mg/m^2 daily, for two days. There is a greater fall of sweat electrolytes in normal than in affected individuals. The test has been evaluated in a few children[12] and also in adults.[13] Further evaluation of this test is needed, but impressive falls in the sweat electrolyte concentrations certainly do occur in unaffected individuals.

Further confirmation that marginally raised electrolyte values are not due to cystic fibrosis involves tests other than estimation of sweat electrolytes. These additional investigations have been reviewed elsewhere and include the exclusion of both malabsorption and a pancreatic lesion.[14]

Basis of diagnostic mistakes

Misdiagnosis of cystic fibrosis has usually followed one or more false positive sweat tests with subsequent uncritical acceptance of the results by the clinician; also there has usually been a failure to show either intestinal malabsorption by faecal fat estimation or any evidence of a pancreatic lesion. Such diagnostic mistakes are serious and it is suggested that patients considered to have cystic fibrosis who have no evidence of a gastrointestinal lesion should be referred to a cystic fibrosis centre to confirm or refute the diagnosis.

Conclusion

The sweat test remains one of the most important and specific examinations currently affected by the biochemistry laboratory. The test should be carried out on children with recurrent descending respiratory infections, unexplained failure to thrive, recurrent vomiting, chronic liver disease, rectal prolapse, nasal polyps, pancreatitis, and malabsorption.

The practical difficulties and common problems in carrying out the test should be remembered, and only experienced laboratory staff should perform the test. In patients who have caused diagnostic problems and where the sweat electrolyte values are marginal the clinical team and laboratory facilities of a cystic fibrosis referral centre should assist with the diagnostic problem by showing malabsorption and the presence, or absence, of a pancreatic lesion by non-invasive methods, but, if necessary, by a stimulated pancreatic function test.[15] Individuals who have marginal rises in sweat electrolytes that return to the normal range after 48 hours of 9α-fludrocortisone and in whom there is no evidence of either malabsorption or a pancreatic lesion do not have cystic fibrosis.

It must be re-emphasised that the implications of a positive test are so serious that the investigation should only be performed by experienced laboratory staff. The clinician should never diagnose cystic fibrosis on the result of one, or even two, sweat tests but only on the results of these tests in the context of the overall clinical picture.

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The intrauterine hazards of twins

Society is intrigued by twins, and twin children are often the focus of admiring attention. It is not surprising that most parents are proud when they hear that twins are on the way. Many, however, will be disappointed: a large proportion of these parents will never produce the two healthy babies for which they hope.

The vanishing twin

The outcome of many twin pregnancies is a singleton infant. In at least 50% of twin pregnancies one fetus is lost, the majority in the first trimester—the vanishing twin syndrome.[1] It is only since the advent of ultrasound that many of these second fetuses have been detected at all. Now that twin pregnancies are detected very early the question arises about whether to tell the parents immediately and risk a later disappointment. Many parents say they would prefer to know.

For those twins who survive the first trimester there are still many hazards, all of which contribute to the high perinatal mortality and long term morbidity associated with multiple births.

Growth retardation

The average weight of a newborn twin is about 800 g less than a singleton, but if allowance is made for gestational age the discrepancy is reduced to 500 g. The difference in the rate of growth increases through the pregnancy. The growth of the human fetus is influenced by litter size, and the deceleration that occurs at about 36 weeks in singletons takes place correspondingly earlier in twins and higher multiple births.

Even when allowance is made for their slightly shorter gestation monozygotic twins are lighter than dizygotic ones. Nor can this be wholly explained by the reduced efficiency of a monochorionic placenta because dichorionic monozygotic twins also appear lighter than their dizygotic counterparts.[2] A variety of explanations has been proposed for the different growth rates in the two types of twins, including the effects of events in early embryonic development when the cell mass is reduced by division, the possible beneficial effect that antigenic differences between dizygotic twins may have on intrauterine growth, and maternal factors, such as greater height and higher hormone concentrations in dizygotic mothers.[2]

Discrepancies in birth weight are commoner and larger within monozygotic pairs. This is mainly due to the fetofetal transfusion syndrome. Eccentric insertion of the umbilical cord or, in dichorionic pairs, differing sites of implantation of the placenta may also affect the rates of fetal growth.

Congenital anomalies

It is now generally agreed that congenital anomalies are more common in twins than singletons but that this increase is probably limited to monozygotic twins.[3] Several reasons for the increased risk among monozygotic twins have been proposed. These include, firstly, the less favourable environment of a shared placental circulation; secondly, the disruption of the developmental genetic clock of the embryo caused by the zygote division, making the monozygotic embryo more susceptible to subtle environmental agents; and, thirdly, that monozygotic twinning may in itself be a form of congenital malformation.

In addition to anomalies specific to twinning such as conjoined twinning and acardia, there are some conditions that seem to have a particularly high incidence in twins. These include oesophageal atresia, single umbilical artery, and some chromosome anomalies, such as Klinefelter's and Turner's syndromes. These like many other anomalies may occur in only one of a monozygotic pair.

Fetofetal transfusion syndrome

One in four pairs of twins share a fetal blood circulation. In many instances these monochorionic twins harmoniously share a 'third circulation' without apparent ill effect. For some, as in the fetofetal transfusion syndrome, the results may be disastrous.

When no superficial anastomoses are present on the placenta to compensate for the deep arteriovenous blood flow a chronic haemodynamic imbalance may develop and continue for many months, causing not only unequal growth of the fetuses but anaemia and polycythaemia of such severity as to cause death to one or both fetuses. The poor growth of the donor is due to the loss of nutrients together with the haemoglobin to the cotwin. There may also be reduced maternofetal transfer of nutrients and of immunoglobulin G across the grossly abnormal and oedematous placenta.[4] Size and maturity of the fetal organs may differ even more strikingly than body size.[5]

Intrauterine death

About twice as many twins are stillborn as singletons. This is partly due to the problems already described. In other cases the life of one fetus may have to be deliberately risked where, for example, an induced premature delivery would jeopardise the chances of survival for the healthier twin, as in the case of discordant blood group incompatability.

Most twins survive the intrauterine death of their cotwin, physically at least, unharmed. In monochorionic twins, however the survivor may have severe problems from disseminated intravascular coagulation. If one fetus dies early in the pregnancy emboli may disrupt the development of the survivor. Some congenital anomalies, such as cerebral abnormalities, aplasia cutis, and intestinal atresia, may be caused by such ischaemic insults in a twin pregnancy.[6] The presence of a fetus papyraceus or a macerated stillborn twin in a monochorionic pregnancy should always alert the paediatrician to the possibility of a structural defect in the survivor.

The loss of a twin

It is not known how much the early loss of a twin fetus may affect the mother or indeed the single survivor. There is evidence that at least some lone twins have personality problems that could be related to the loss of their twin partner. It may be more important than now realised that both the mother and the surviving child are made aware of the twinship and are offered appropriate support in coming to terms with their loss.[7]

In a dichorionic multiple pregnancy where one fetus is abnormal the new option of selective feticide is now available to parents who would otherwise have to choose between terminating the pregnancy despite the sacrifice of a normal baby or continuing the pregnancy while knowingly carrying an abnormal child.[8] Couples who undergo selective feticide must cope not only with their bereavement but also with the stress of carrying a dead fetus for many weeks and later of explaining to the surviving twin what has happened.

It is now recognised that parents who have a stillborn twin face very particular problems.[9] They have to experience the joy of a new baby and the tragedy of a death simultaneously. Because they still have a live infant their loss, if acknowledged at all, is usually greatly underestimated. They are encouraged to attend to the live baby and often discouraged from talking about the dead baby. This can lead to unresolved mourning, the idealisation of the dead child, and sometimes to a definite rejection of the survivor. Such parents may have difficulty in distinguishing the two babies in their minds. Some may feel the dead one never existed—a fantasy baby. Substantive memories, such as photographs or even an ultrasound scan showing the two babies together, can help to clear the emotional confusion. Naming the baby not only helps to distinguish the babies but later makes it easier when talking to the surviving child about his twin.

It should also be recognised that the parents have in the survivor a lasting reminder of the child that might have been. Birthday celebrations are coupled with painful memories of the death. All parents should be offered expert counselling not only during their own bereavement but later if they have to cope with the often complex feelings of a child deprived of its close partner.

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Current state of theophylline in asthma

Until about 1975 theophylline was used in this country for the treatment of asthma almost exclusively as intravenous aminophylline. With the introduction of oral preparations theophylline came onto the market to compete with the beta agonists, sodium cromoglycate and beclomethasone. Their introduction was also coincident with the age of the clinical trial—some would say the age of the poor clinical trial—and theophylline has been compared with almost every other drug for asthma in what seems to be every possible permutation. Those who have escaped involvement in the trials will not have escaped the marketing. In this country there are no fewer than five slow release, two liquid, and two tablet preparations suitable for children. As not all are 100% theophylline dosage, when translated into patient oriented language of mls and pills, becomes an exercise of memory and arithmetic.

Does theophylline work?

There is no doubt that theophylline is an efficient bronchodilator, but how it works is unknown. It has little effect on bronchial responsiveness to nonspecific agents such as histamine[1] and is only moderately effective in blocking exercise induced bronchospasm.[2] In patients with asthma improvement in lung function is significant when serum concentrations reach 5 μg/ml and correlates with the logarithm of concentrations between 5 and 20 μg/ml.[3] The response is variable between individuals.

How does theophylline compare with other drugs?

Studies that have compared theophylline with the beta agonists have produced conflicting results. One reason for this is the different dosages, duration of action, and routes of administration of the preparations of beta agonists used. The impression is that they compare favourably. Either would be suitable when the continuous treatment of asthma with oral drugs is considered most appropriate—in very young children, for example.[4] Certainly, they have an additive effect, a property made use of in the hospital management of acute asthma but that can also be exploited in the prevention and management of acute wheezy episodes as home. It seems sensible to start a beta agonist and add theophylline if necessary at the beginning of an upper respiratory tract infection in a child who is likely to become very wheezy. Theophylline also compares very well with cromoglycate[5] but is not as good as beclomethasone.[6] In some patients with particularly troublesome asthma the addition of theophylline to beclomethasone will improve control. Many patients may be satisfactorily controlled during the day on whatever treatment but are still disturbed by nocturnal symptoms and it is for these that a slow release preparation taken before bed may well be beneficial.[7]

What value is there in monitoring serum concentrations?

Much has been written about this vexed subject. Blood concentrations are easy to measure, and recently there has been introduced a fingerprick method for bedside use (Acculevel, Syva). This is likely to be of most use in planning aminophylline treatment in patients with acute asthma who have already taken theophylline. Unfortunately, salivary concentrations, under normal circumstances of collection, do not correlate well enough with serum concentrations to be of clinical value.[8]

Pharmacodynamic uncertainties. Absorption and bioavailability of some commonly used preparations are severely affected by food in the stomach,[9] and it is possible that factors that affect gastric emptying, such as exercise, also affect absorption. The interpatient variation in half life—1·5–10·5 hours—is well known.[10] There is also appreciable intrapatient variation over a period of one to nine months,[11] but how much variation there is from day to day in the paediatric outpatient is unknown. There is evidence in both adults and children that timed serum concentrations during the elimination phase may vary considerably.[12 13] In addition, elimination rates are prolonged by many other factors, among them the presence of viral infections—notably, influenza—and treatment with erythromycin.[14]

Thus it seems that single measurements of serum theophylline are of little value. Even a carefully timed profile of concentrations measured in hospital may not accurately reflect the day to day profile in a child who may not have a reproducible day to day lifestyle.

When should a profile of concentrations be measured? Dosages of commonly available preparations that are most likely to put patients' concentrations within the correct range have been worked out.[15] On such dosages concentrations much in excess of 20 μg/ml are unlikely under normal circumstances and in excess of 35 μg/ml, above which life threatening side effects can occur, quite improbable. Patients whose asthma is satisfactorily controlled in this way—that is, without a profile of blood concentrations—should be made aware of situations when their concentrations will possibly rise and cause nausea—for example, during an upper respiratory tract infection.

If the dosage does not produce a therapeutic result—that is, the asthma is not controlled—the clinician has two choices: he can either admit the child for a profile, remembering the difficulties in interpreting such a profile, and increase the dosage if necessary (after which he should logically do another profile) or he can simply change the drug. Patients with severe asthma in whom manipulation of drugs has failed to effect adequate control are the most likely candidates for the 'tailoring' of theophylline dosage. Ideally, this should be done under conditions of diet and activity most resembling those of everyday life.

Side effects

Severe toxicity in children, with convulsions, coma, and haemorrhage, which can clearly be ascribed to theophylline, seems to occur only when the usual dose has been exceeded or when aminophylline has been given in addition.

It is the clinical impression that theophylline, even when concentrations are below 20 μg/ml, is associated with nausea and vomiting. In a double blind study comparing cromoglycate with theophylline where patients were informed beforehand what side effects might occur[5] there was surprisingly little difference between the two groups in the reporting of side effects usually attributable to theophylline, although it has to be admitted that the number of patients was very small. What is more worrying than nausea or vomiting, which may well stop the patient taking the drug or the clinician prescribing it, is the risk of side effects such as changes in concentration and sleep disturbances, which may interfere with schooling and which cannot so easily be attributed to the drug.[16] As theophylline is a drug closely related to caffeine, which has well described psychotoxic side effects in susceptible subjects, it seems on a pharmacological basis that anxieties are not unreasonable.[17] It would seem to be a matter of some importance, if theophylline is to continue to be widely prescribed, that the possibility of this side effect is more carefully examined. The problem is that designing a trial to evaluate such side effects properly would be likely to be a very difficult undertaking.

Conclusion

Although theophylline is an invaluable bronchodilator in the management of acute asthma, it has many limitations when considered for use in the day to day management of continuous asthma. Single measurements of serum theophylline are of limited value and it would seem that the tailoring of dosage may not be as straightforward as previously supposed. There seems to be sufficient concern about the incidence of side effects to suggest that theophylline should not be the drug of first choice for the management of continuous asthma when other less troublesome drugs are available. Theophylline does, however, have a clear place as a supplement to other drugs in the management of patients with severe asthma and in the management of nocturnal asthma when symptoms cannot be otherwise controlled.

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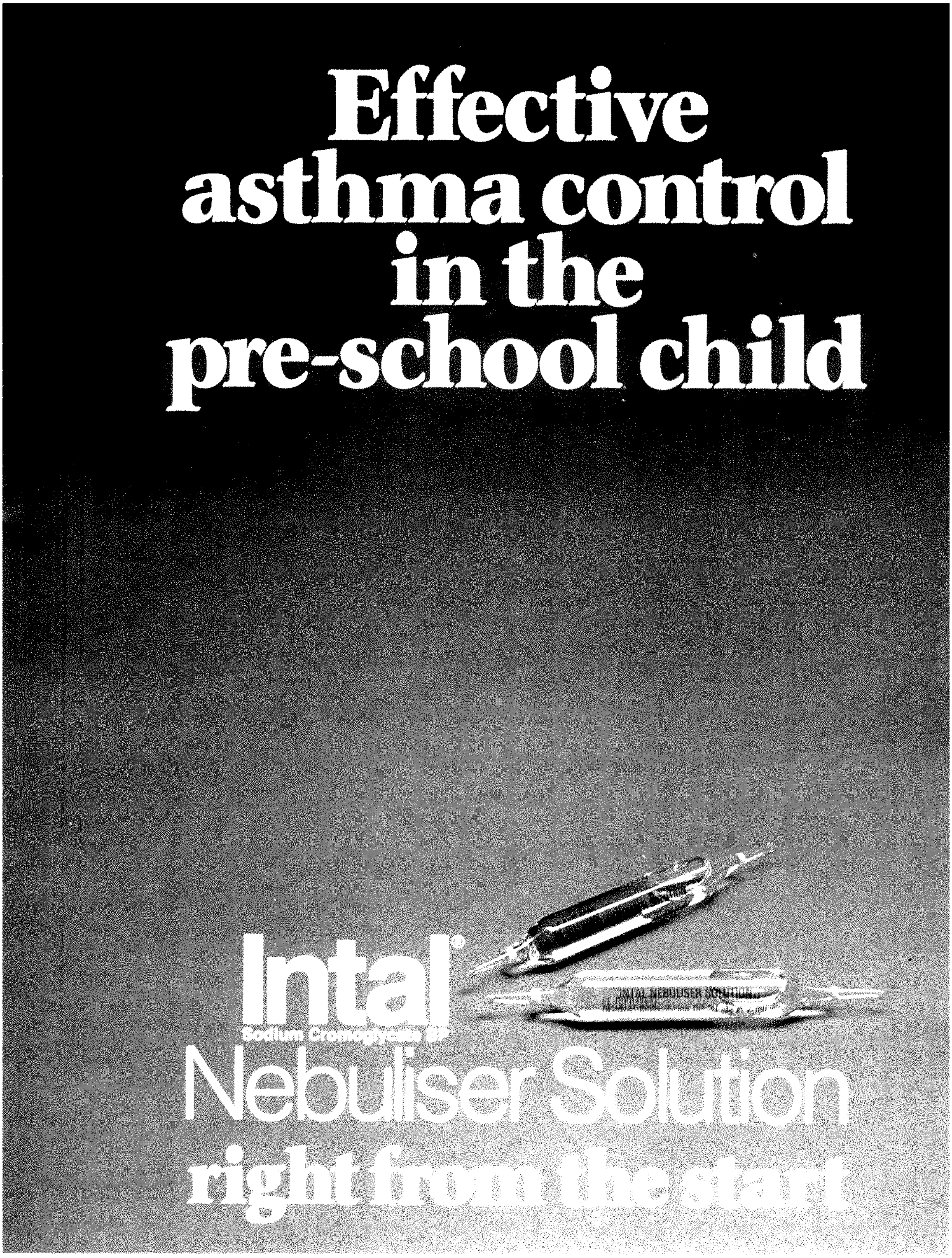

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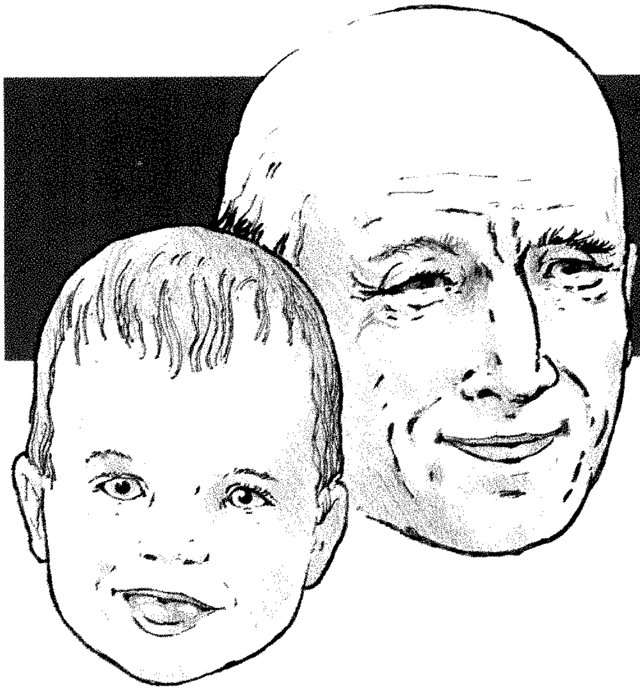

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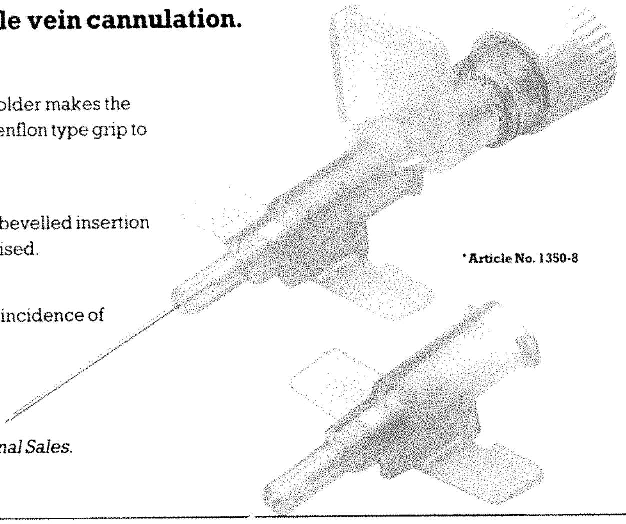

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Original articles

Growth and childhood asthma

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SUMMARY Height and weight were measured every six months in a long term prospective study of 66 children with chronic perennial asthma for a mean 13·1 years. There was no evidence of growth retardation on entry into the study. Growth developed along normal lines in all 66 children until about 10 years, and in 35 of these children growth continued along normal lines throughout the whole period of follow up. Thirty children showed the physiological decelerating growth velocity pattern seen in children with delay in the onset of puberty, and one child had an early menarche. The tendency for delay in the onset of puberty was significant for both boys and girls and was noted to be independent of severity of asthma. Once puberty finally began in these children, complete catch up growth resulted in the attainment of the predicted adult height. Long term prophylactic inhalation of beclomethasone dipropionate in 26 children in a dosage up to 600 mcg/day before puberty and 400 mcg/day during puberty was shown not to affect growth.

It is concluded that asthma had no direct influence on growth in height but was associated with delay in the onset of puberty. The pre-adolescent physiological deceleration of growth velocity that occurs in these children gives the impression of growth retardation.

Since growth retardation in childhood asthma was first described by Cohen *et al* in 1940[1] there have been many conflicting views concerning its occurrence. Some workers have noted growth retardation only in those children treated with corticosteroids,[2 3] while others have related it to the severity of asthma.[4 5] The observation that bone age was retarded to the same extent as height suggested that the short stature was associated with developmental delay and led to the prediction that these children would ultimately grow to normal heights.[6 7] This was supported by Ferguson *et al,* who also noted that short stature was three times more prevalent in children with allergic respiratory disease than the general population.[8] They emphasised, however, that it was *not* related to the severity of asthma and was equally apparent in children suffering from allergic rhinitis only.

It is not disputed that growth retardation develops in children with asthma treated with regular oral corticosteroids,[9 10] and it was an important advance in this form of treatment when it was shown that if given as a single dose on alternative days adequate control of asthma was possible without growth impairment.[11] Recently, the use of aerosol steroids in children has been shown to be effective and safe, while allowing children to grow along expected lines,[12] although this too has been questioned.[13]

To clarify the effect that the disease and treatment has on growth, the opportunity has been taken during a long term prospective follow up study of children with chronic perennial asthma[14] to observe the growth pattern throughout childhood and adolescence of 29 children treated with corticosteroids and 37 children who never received treatment with steroids.

Subjects

Thirty eight children with chronic perennial asthma were seen at six monthly intervals for a mean of 8·9 years in a prospective study designed to observe the relation between childhood asthma and puberty.[14] Recently, 32 of these patients have been traced and their final adult heights and the heights of their parents obtained. Of the remaining six patients, one had died aged 13·7 years in an acute attack of asthma and the other five could not be found.

A further 28 patients who attended the Paediatric Asthma Clinic at the Hammersmith Hospital have been added to the original group. All 28 parental heights were known and all were seen at least every six months by the author from middle childhood, through puberty until reaching their final adult heights. In many it has been possible to review their clinic records from an early age, giving a consistent follow up of their growth and progress for nearly 20 years. Thus mean age of entry to this study for all 66 children was 7·5 years (1·9–12·1 years) and mean age when last reviewed was 20·6 years (12·8–25·9 years), giving a mean period of follow up of 13·1 years.

The 66 children were grouped as previously;[14] 29 children who could not be controlled by sodium cromoglycate and needed treatment with steroids; 33 children who could not be controlled by bronchodilators alone and were successfully treated with sodium cromoglycate; and four children successfully controlled by bronchodilators alone. The group successfully treated with sodium cromoglycate were further subdivided into 19 children who showed no improvement in their asthma before the onset of puberty (subgroup A) and 14 children who improved before the onset of puberty (subgroup B). As the group treated with bronchodilator consisted of only four children and has been shown previously to have a similar prognosis to subgroup B of the group treated with sodium cromoglycate,[14] these two groups have been combined when comparing the severity of asthma.

Methods

Anthropometry. Height was measured standing with heels and back in contact with the vertical measuring column. Gentle pressure was applied beneath the mastoid process and the head was held so that the lower border of the eye socket was in the same horizontal plane as the external auditory meatus.

Weight was measured without coat and shoes.

Estimation of growth. Height and weight were recorded on longitudinal growth and developmental charts prepared by J M Tanner and R H Whitehouse for the Hospital for Sick Children, London. They were measured at each six monthly visit. The pattern of growth corresponding to the height and weight centile was apparent for each child (Fig. 1), and by extrapolation it was possible to predict the expected height and weight of each child at the end of the study. The effect that severity of asthma, treatment, and delayed puberty had on growth could be seen by noting any deviation from the established centile pattern. By comparing the predicted heights and weights of the children with the actual heights and weights finally attained, the effect of childhood asthma on growth could be directly observed.

Sixty of the 66 children were followed into adult life until growth was complete. Comparison of their final heights with their predicted heights from the centile chart was supported by comparing their final heights with the heights of their parents. In addition, 24 of these 60 children had their left wrist and hand *x* rayed soon after entry into the study. Skeletal maturity and prediction of adult height by the TW2 method[15] was assessed in the 24 children and compared with the actual adult height obtained.

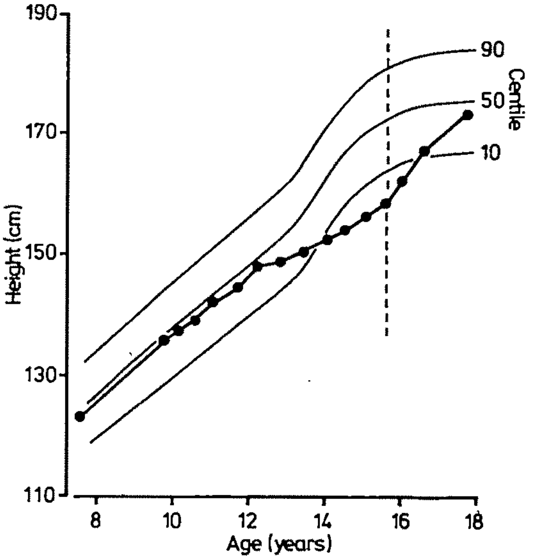

Fig. 1 *Height record on a Tanner and Whitehouse growth and development chart (10th, 50th, and 90th centile lines) for a child illustrating:*
(1) the established centile pattern from 7·7–12·3 years;
(2) the physiological decelerating growth velocity pattern of delayed puberty;
(3) the puberty growth spurt, resulting in the child regaining his original height centile.
The broken line represents the onset of puberty.

The remaining six children who were lost to the study before their final adult height was known were followed up to a mean 8·3 years (6·3–14·6 years). Thus the effect of the illness on their pattern of growth was well observed and in four was supported by comparison of the chronological age with the bone age estimated from a radiograph of the left wrist before the onset of puberty.

Onset of puberty. A physical examination was performed at each visit. The beginning of puberty was defined as the first sign of a secondary sexual characteristic, either the initial enlargement of the genitalia in boys, a breast bud in girls, or pubic hair in both. The age at which this sign was noted was accepted as the age of onset of puberty and was accurate to within six months.

Analysis. The results were analysed by use of paired and unpaired Student's *t* tests.

Results

None of the 66 children on entering the study were below the 3rd centile and most (40/66) were above the 50th centile (Fig. 2). Distribution of the separate groups did not indicate an initial relation between severity of asthma and growth retardation with respect to height. On the contrary, it should be noted that on entering the trial 19 of the 29 children in the group treated with steroids had a height centile above the 50th centile.

From then until about 10 years of age all 66 children grew along their expected centile lines without appreciable deviation, irrespective of the severity of asthma or treatment. Thirty five of the 66 children continued to grow along their expected centile lines without appreciable deviation throughout the whole period of follow up, 30 showed the physiological decelerating growth velocity pattern seen in children with delay in the onset of puberty (Fig. 1), and one showed the rapid deceleration in growth that follows an early menarche. She was the only child in this study who failed to grow to within five per cent of her expected height. Her height remained consistently on the 97th centile despite severe perennial asthma controlled by regular treatment with aerosol steroids for 4·4 years. Pronounced growth deceleration followed an early menarche, at which time she no longer took corticosteroids and had virtually recovered from her disease. In contrast, the 30 children with the delayed growth pattern were observed to catch up dramatically once puberty finally began.

In the 60 children whose final adult heights were known no significant difference was detected between the heights predicted from the extrapolated centile line and the final adult heights in either the 41 boys (t=1·03) or the 19 girls (t=1·35). Nor was any significant difference detected when comparing the three treatment groups: the group given steroids, the subgroup A given sodium cromoglycate, and the combined subgroup B given sodium cromoglycate and group given bronchodilator (Fig. 3). Both the boys and girls grew well in comparison to their parents (Table 1), and the mean parental heights were comparable with the accepted norms for this country.[16] Moreover, the mean mid-parental

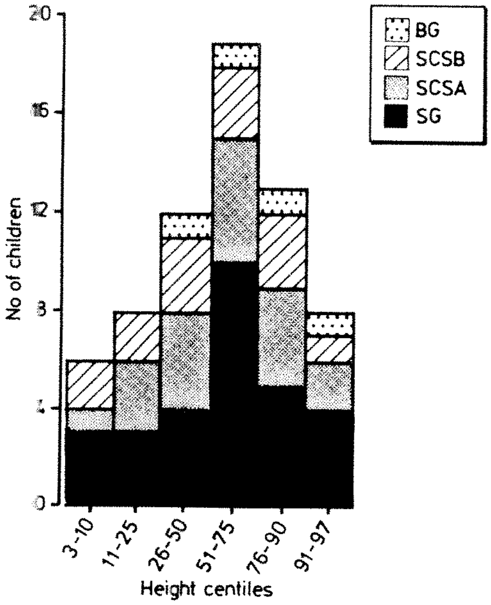

Fig. 2 *Height centile of each child on entering the study, indicating group distribution. SG=group given steroids; SCSA=sodium cromoglycate subgroup A; SCSB=sodium cromoglycate subgroup B; BG=group given bronchodilator.*

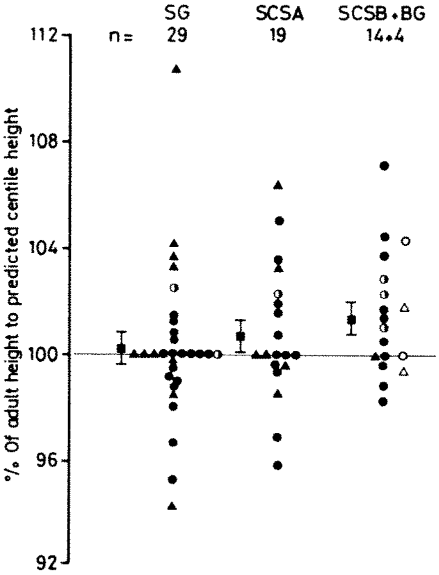

Fig. 3 *Final adult height as a percentage of the height predicted from the extrapolated centile line in 60 children (●=boys, ▲=girls), and height last seen as a percentage of predicted centile height in six boys not seen as adults (◑). Comparison between the group given steroids (SG), the sodium cromoglycate subgroup A (SCSA), and the sodium cromoglycate subgroup B + group given bronchodilator (the four open symbols) (SCSB+BG) was not significant in any pairing.*

Table 1 *Final adult height in relation to parental height in 60 children with asthma. Values are mean (SD)*

Sex	*n=*	*Height (cm)*			
		Final	*Paternal*	*Maternal*	*Mid-parental*
Boys	41	177·7 (6·0)	174·4 (5·9)	160·8 (5·7)	167·6 (4·5)
Girls	19	164·3 (7·1)	175·3 (9·3)	161·1 (5·8)	168·2 (6·7)

Table 2 *Final adult height in relation to height predicted from prepubertal bone age in 24 children with asthma with information on bone age. Values are mean (SD)*

Sex	*n=*	*Height (cm)*		*p Value*
		Final	*Bone age predicted*	
Boys	15	180·0 (5·4)	174·9 (6·2)	<0·005
Girls	9	163·1 (4·7)	161·3 (5·2)	Not significant

Table 3 *Relation between height and weight in 66 children with asthma on entering the study*

Group	*n=*	*Height centile greater than weight centile*	*Height centile equal to weight centile*	*Height centile less than weight centile*
Steroid	29	20	6	3
Sodium cromoglycate subgroup A	19	7	6	6
Sodium cromoglycate subgroup B + bronchodilator	18	8	3	7
Total	66	35	15	16

heights were extremely close to the value of 168 cm found in the Harpenden growth study.[17]

In the 24 children where it was possible to compare the predicted final height determined from the bone age measurement with the actual final adult height (Table 2) there was no significant difference for the girls. The boys' final adult height was, however, significantly greater than the final height predicted from bone age ($p<0\cdot005$).

When last seen, the heights of the six children whose final adult heights were not obtained were either equal to or slightly greater than their heights predicted from the extrapolated centile line (Fig. 3). Four of these children had bone age assessments; three were equivalent to their chronological ages and one, a boy whose onset of puberty was delayed until 14·2 years, was retarded by 2·6 years.

Growth in weight generally followed the same pattern as height, but with much broader variations. Many of the children in their teens, especially the boys, gained an excessive amount of weight, while some of the girls were difficult to assess as they lost weight dieting, one developing anorexia nervosa. Comparison of the weight centile with the height centile on entering the study did show, however, that those children most severely affected by the disease, in the group given steroids, tended to be underweight (Table 3). To determine whether poor weight gain influenced the delay in the onset of puberty, the 35 children who were underweight on entering the trial were compared with the 31 children who were not. The mean (SD) age of onset of puberty for the boys was 13·5 (1·5) and 13·3 (1·3) years, respectively, and for the girls was 12·5 (1·2) and 12·4 (1·0) years, respectively. The differences were not significant.

Group treated with steroids. The 29 children in this group divided into three children treated with intermittent courses of oral prednisolone and 26 children treated with prophylactic aerosol inhalation of beclomethasone dipropionate for a mean of 5·8 years (1·1–12·3 years).

The three children on intermittent treatment with steroids, six children whose dosage of beclomethosone dipropionate did not exceed 400 mcg, and nine children whose dosage of beclomethasone dipropionate reached 600 mcg, five for longer than two years, grew along expected lines unaffected by their treatment. Eleven children whose dosage of beclomethasone dipropionate exceeded 400 mcg did seem to show inhibition of height growth, but only during the immediate pre-adolescent period of delayed puberty when growth velocity naturally falls. All 11 children regained their predicted height during the subsequent growth spurt.

Delayed puberty. It became apparent while charting the growth of the children in this study that there was a considerable number whose growth rate followed the physiological decelerating velocity pattern seen with delayed puberty (Fig. 1). In 21 of the 47 boys and four of the 19 girls the onset of puberty was delayed beyond the 95% confidence limits of Marshall and Tanner[18 19] (Fig. 4), and the mean age of onset of puberty was significantly delayed in both the boys ($p<0\cdot001$) and the girls ($p<0\cdot001$). There was no significant difference, however, between the treatment groups, showing that this delay in puberty was independent of the degree of severity of their illness.

Discussion

This long term follow up of 66 children with chronic perennial asthma has supported previous observations that weight gain tends to be reduced depending

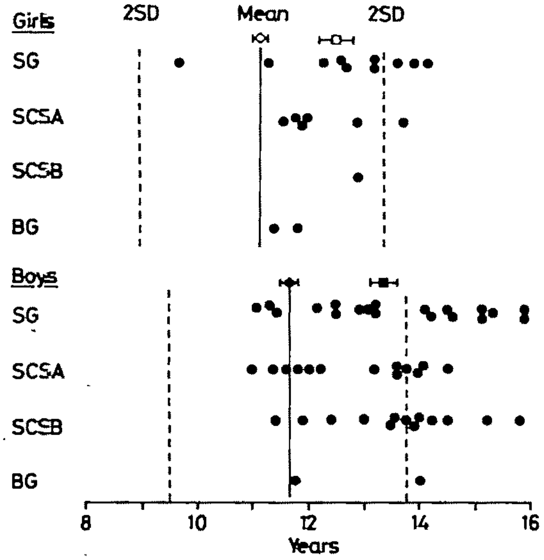

Fig. 4 *Age (in years) at which onset of puberty was first detected in 47 boys (mean 13·4 (SE 0·2)) and 19 girls (mean 12·6 (SE 0·3)) plotted against their respective groups.*

The mean age and 2SD lines are shown indicating the first sign of puberty noted by Marshall and Tanner:

Girls[18]*=breast development (mean 11·2 (2SD 2·2) (SE 0·1));*

Boys[19]*=genital development (mean 11·6 (2SD 2·1) (SE 0·1)).*

Comparison of the group given steroids (SG), sodium cromoglycate subgroup A (SCSA), and sodium cromoglycate subgroup B (SCSB) + group given bronchodilator (BG) in the boys showed no significant difference in any pairing, nor was any significant difference noted between the group given steroids and sodium cromoglycate subgroup A in the girls. There were too few in the remaining group for comparison.

on the severity of the disease.[20] Growth in height was shown, however, to be unaffected by asthma, although the incidence of delayed puberty was significantly increased. This confirmed the impression gained from previous studies that growth retardation was related to the physiological decelerating growth velocity pattern of delayed puberty, and after the onset of puberty the subsequent catch up growth resulted in the attainment of the predicted adult height. Thus the conflicting reports of an association between growth retardation and asthma in the past were probably due to the age at which the children were studied. Investigators who examined mainly younger children, below 10 years of age, would have found no growth retardation, whereas those studying older children, 10–15 years of age, would have discovered a definite association.

Three of the studies in which no growth retardation was found were longitudinal (Table 4), the most reliable method of observing growth. Although two are for fairly short periods, with no mean age given, Spock's follow up of 200 children for a minimum of three years suggests they were seen before the delayed puberty growth pattern developed.[3]

Of the studies that claimed growth retardation, all those carried out cross sectionally must have included children with delayed puberty. In McNicol and Williams' longitudinal study children were examined at three specific ages—7, 10, and 14 years.[5] [20] No growth retardation was found up to the age of 10 but was noted at 14. As children still showing signs of disease at 14 years were included in their more severe group it was assumed that asthma was the cause of the growth retardation. They also reported growth retardation in a further 56 children examined cross sectionally between the ages of 10

Table 4 *Comparison of studies of growth retardation in children with asthma*

Authors	*Study*	*No of patients*	*Age range (yrs)*	*Mean age (yrs)*
Studies showing growth retardation				
Cohen *et al*[1]	Longitudinal	5	9·17	?
Cohen *et al*[21]	Longitudinal	150	?	?
Snyder *et al*[6]	Cross sectional	91	1·5–15	7·6
Dawson *et al*[4]	Cross sectional	121	10–15	12·1
McNicol and Williams[5]	Longitudinal	314	7:10:14	Martin *et al*[23] at 21
Murray *et al*[22]	Cross sectional	183	7–20	10·0
Hauspie *et al*[7]	Mixed longitudinal	531	2–20	?
Chang *et al*[24]	Cross sectional	231	6·2–16·2	11·5
Ferguson *et al*[8]	Cross sectional	598	3–17	?
Studies showing no growth retardation				
Van Metre *et al*[10]	Longitudinal (10 months or more)	52	?	?
Falliers *et al*[2]	Longitudinal (6 months or more)	270	5–16	?
Spock[3]	Longitudinal (3 years or more)	200	4–12	7·0
Klein *et al*[25]	Cross sectional	20	4–15	?

and 12 years whose asthma was severe enough to cause chest deformity.[26] Yet when Martin *et al* reviewed all McNicol and Williams' cases at the age of 21 years, they noted that complete catch up growth had occurred, as observed in the present study.[23]

Hauspie *et al* in their mixed longitudinal study also stated that height growth retardation was related to the degree of severity of asthma.[7] They considered that the retarding effect on growth caused the delay in the onset of puberty, with the subsequent catch up growth apparently overcoming all previous effects of the disease. They speculated that the growth retardation could have been due to various factors suggested in the past: respiratory insufficiency with hypoxia,[22 27] inadequate nutrition,[28 29] chronic or recurrent infections,[6 30] long term stress,[7] and suppression of normal activity.[27] The opportunity for close long term observation in this study has made it possible to discount all these factors, particularly as all the children were given treatment specifically aimed at keeping them well enough to lead a normal life on a minimum of treatment.

The two studies by Cohen *et al* were also longitudinal, but the first consisted of only five cases,[1] two of whom had merely nasal allergy and only one of whom had moderately severe asthma. They made the interesting observation that 'active treatment', indicating desensitisation, soon cured the growth retardation. They emphasised this eight years later with a further 150 cases, but with no details of their age range.[21] The importance of these studies was their description of growth retardation in children with mild respiratory allergy, many without asthma. This observation has been reported recently by Ferguson *et al*, who noted growth retardation independent of the severity of the disease and stated that the basic problem was the atopic state.[8] Whereas that group of workers emphasised that it affected 'growth regulation', however, this present study would suggest the effect was primarily on the mechanism responsible for the 'switching on' of puberty itself. The regulation of height growth has been shown to be normal in all 66 children followed up. The only deviation from the established centile pattern has been the pre-adolescent deceleration in growth velocity seen in the children with delayed puberty, and this is physiological. Tanner has described this period as having the 'lowest growth velocity ever experienced' and talks about the immediate pre-adolescent velocity being so low that parents sometimes allege, mistakenly, that the child has actually stopped growing altogether for a year or more'.[31] It is the large number of children with asthma with delayed puberty exhibiting this pattern that gives the impression of abnormal growth retardation.

It has been shown that effective treatment was possible with regular inhaled steroids without affecting growth.[12] These observations were supported in this study. Before the onset of puberty, dosage of beclomethasone dipropionate up to 600 mcg/day has been compatible with a normal growth velocity, and up to 400 mcg/day has been given during puberty without impairing the growth spurt. With the expected improvement in childhood asthma that has been shown to occur during puberty,[14] it should rarely be necessary to exceed this dose on a regular basis. Thus it should be possible for all children with asthma to attain their normal predicted height.

Conclusion

In this prospective study of children with asthma all grew normally until about 10 years of age, and all ultimately reached their predicted adult height, showing that asthma had no effect on growth in terms of height. A considerable number, irrespective of the severity of asthma, had delay in the onset of puberty, and it is suggested that the pre-adolescent physiological deceleration of growth velocity that occurs in these children is the reason that asthma has previously been considered to cause growth retardation.

I thank Dr Michael Silverman and Professor Simon Godfrey for their help and advice over the many years of this study, Miss Margaret Rehahn for help with statistics, Mrs Jane Fallows for the medical illustrations, and Miss Karen Fox for typing the manuscript.

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Sleep apnoea during upper respiratory infection and metabolic alkalosis in infancy

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SUMMARY Three to four hour polygraphic sleep studies were carried out in 10 infants, five with upper respiratory infection and five with metabolic alkalosis secondary to vomiting during and after recovery from illness. During upper respiratory infection, the main abnormality detected was brief (>3<6 seconds) or prolonged (>6 seconds) attacks of obstructive apnoea. Other indices of apnoea were similar to recovery data. Gross body movements were also increased. In infants with metabolic alkalosis indices of central apnoea were significantly increased when compared with recovery or case control data. Prolonged (>15 seconds) attacks of central apnoea and obstructive apnoea (>6 seconds) were only observed during illness. Gross body movements and periodic breathing were also increased.

These findings suggest that the functional consequences of apparently 'mild' illnesses in young infants may be greater than is generally suspected and perhaps relevant to mechanism(s) of death in sudden infant death syndrome.

Most infants have minor symptoms at some time during the early weeks of life but recover uneventfully. Several investigators observed an increased frequency of such symptoms before death in victims of sudden infant death syndrome.[1–4] Fifty nine per cent of the 145 victims of the syndrome studied by Stanton *et al* had recent symptoms, predominantly respiratory, compared with 16% of 154 controls.[5] The questions arise whether 'minor' illnesses trigger a fatal sequence of events in a predetermined group of infants with altered responsiveness or whether age and maturity increase susceptibility in all infants from which a subgroup succumbs. The nature and severity of naturally occurring stresses that cause minor symptoms have received little attention. We have investigated the cardiorespiratory effects of natural stresses (upper respiratory tract infection and metabolic alkalosis caused by vomiting) in normal infants in the age group at risk for sudden infant death syndrome. The infants were not considered at increased risk in other aspects.

Patients and methods

Two groups of infants were studied during and after recovery from symptoms—one group with upper respiratory infection and the other with recurrent vomiting.

Groups studied.

Group 1: respiratory tract infections
Five infants were studied during and after recovery from upper respiratory tract infection. Four were born at term after uncomplicated pregnancies and deliveries; the fifth was born at 29 weeks' gestation after premature rupture of the membranes. There were four boys and one girl, with a mean gestation of 38 weeks (range 29–41 weeks) and a mean birth weight of 2630 g (range 1290–3460 g). Mean chronological and postconceptional ages were 8 weeks (range 4–15 weeks) and 46 weeks (range 44–49 weeks), respectively, when initial studies were carried out. The mean interval between illness and recovery studies was 22 days (range 13–46 days). Initially, the infants had coryzal symptoms but were otherwise well. At follow up they were healthy and thriving. Mean rectal temperature was 36·9°C (range 36·4–37·5°C) during infection and 36·8°C (36·5–37·2°C) after recovery. There were no signs of respiratory distress on either occasion and on auscultation breath sounds were vesicular without

accompaniments. Immunofluorescent studies of nasopharyngeal secretions confirmed respiratory syncytial virus infection in one infant.

Group 2: recurrent vomiting

Five infants with a history of recurrent vomiting of duration of four to 21 days were also studied before and after pyloromyotomy for congenital hypertrophic pyloric stenosis. They had been born after uncomplicated pregnancies and deliveries. All were boys, with a mean birth weight of 3270 g (range 2690–3770 g) and a mean gestation of 39 weeks (range 36–40 weeks). Mean chronological and postconceptional ages were 5 weeks (3–7 weeks) and 44 weeks (39–47 weeks), respectively, when initial studies were carried out. The mean interval between studies was nine days and between surgery and follow up studies was seven days (range 3–11 days).

Pyloric stenosis was suspected on clinical grounds in each infant at the time of admission to hospital and confirmed by palpation of a pyloric tumour during a test feed. In each case the degree of dehydration was judged to be less than 5% of body weight and intravenous administration of fluid and electrolytes was not deemed necessary to correct fluid and electrolyte inbalance. Table 1 gives serum electrolytes and blood urea concentrations and acid base state in individual infants when initial studies were conducted. One infant, case 1, was hypokalaemic, but otherwise electrolyte and blood urea values were remarkably normal. All infants showed moderate metabolic alkalosis. At follow up clinical recovery was apparently complete. Serum electrolyte and blood urea concentrations had become normal after treatment, and bottle feeding had been satisfactorily resumed in each case.

Infants in the above groups served as their own controls. In addition, five healthy, normal infants matched for age, sex, and postconceptional age were selected as a case control group for infants with recurrent vomiting because of the possibility that index infants had not fully recovered from the metabolic upset associated with recurrent vomiting at the time of follow up studies.

Monitoring procedures. These have been described previously.[6]

Polygraphic sleep studies were carried out in hospital after the last evening feed, usually between 2300 and 0400 h. For follow up studies infants were re-admitted on the preceding afternoon. They were monitored in a dimly lit side room off the main ward, especially equipped for sleep studies. Ambient temperature ranged from 22–25°C. Electrodes were placed in position when the infant had settled after a feed, and nasal thermocouples were applied during periods of quiet sleep. Each infant, lightly clothed and unrestrained, was observed constantly and body movements and interventions recorded on polygraphic paper. Electroencephalogram, electro-oculogram, electromyogram, electrocardiogram, chest and abdominal movements, and nasal airflow were recorded on a Mingograf recorder at a paper speed of 10 mm per second. Sections of recording in each sleep state were also recorded at a rate of 100 mm/second to observe electroencephalogram changes more closely. Permanent records were thus available for electroencephalogram, electro-oculogram, electromyogram, electrocardiogram, nasal airflow, and chest and abdominal movements.

Data analysis. Each 30 second period (one epoch) of the record was analysed visually and sleep state coded according to the criteria of Anders *et al*[7] and those of Rechtschaffen and Kales.[8] The age range of the subjects was such that in some infants the transition between perinatal and 'infantile' sleep pattern[9] might not have been completed. Individual proportions of the electroencephalogram frequencies and amplitudes during the sleep stages were used rather than absolute limits. Respiration, the variable under study, was omitted from the criteria

Table 1 *Serum electrolytes and blood urea concentrations and acid base states of infants with pyloric stenosis*

Case No	*Serum electrolytes (mmol/l)*			*Blood urea (mmol/l)*	*Acid base state*			
	Sodium	*Potassium*	*Chloride*		*pH*	*Carbon dioxide tension (kPa)*	*Subtype bicarbonate ion (mmol/l)*	*Base excess (mmol/l)*
1	138	2·4	—	5·0	7·53	7·35	40·6	+21·6
2	138	3·7	94	3·3	7·49	5·87	35·0	+11·0
3	136	3·6	86	5·6	7·49	5·70	34·0	+9·5
4	139	4·3	98	4·4	7·48	5·25	29·3	+6·6
5	138	3·4	96	3·7	7·50	5·57	30·9	+8·8

of the sleep stages. These were identified as quiet sleep, active sleep, and indeterminate sleep.

The respiration rate and heart rate were counted during the fourth, middle, and last minutes of continuous sleep for quiet and active sleep. Mean respiration rate and heart rate for each sleep state was then computed for each patient during and after recovery from illness and for each control infant. Central apnoeic pauses were defined as periods when chest and abdominal movements were absent and airflow at the nostrils had ceased for at least six seconds. Obstructive apnoea refers to periods during which there was stopping of airflow at the nostrils and continuing (often exaggerated) movements of the chest or abdomen, or both, not begun by gross body movements detected by direct observation or electromyogram recording. This latter proviso ensured that episodes of apparent obstructive apnoea begun by movement[10] were excluded from analysis. The occurrence of prolonged (>15 seconds) attacks of central apnoea[11] and brief (>3 and <6 seconds) or prolonged (>6) attacks[12] were also noted. Indices of apnoea were assessed for central apnoeic pauses greater than six seconds. Apnoea index was defined as the duration of attacks of apnoea (seconds) during a given sleep state divided by the total duration of that sleep state expressed as a percentage. Rate of attacks of apnoea was the number of attacks of apnoea in each 100 seconds of a sleep state, and apnoea per cent was the percentage of epochs during which at least one apnoeic pause was begun. For each sleep state the mean duration of apnoeic pauses was calculated and the attack of apnoea of longest duration noted. These variables were computed for each sleep state and total sleep time. The percentage of time in each sleep state was also noted.

The occurrence and duration of periodic breathing, defined by Parmalee *et al* as two attacks of apnoea of three seconds or more within 20 seconds of each other,[13] and gross body movements were computed in relation to sleep state and total sleep time.

Statistical analysis. The Wilcoxon matched pairs signed rank test was applied to the results obtained during and after recovery from illness in both groups of infants. The Mann-Whitney U test was applied to results obtained for infants with metabolic alkalosis and their matched case controls.

Results

Group 1: respiratory tract infections. Table 2 gives the results for apnoea variables, per cent sleep, respiration rate, and heart rate in relation to sleep phase in the five infants during and after recovery from upper respiratory tract infection. With the exception of respiration rate, which was slightly but significantly increased after recovery, no significant differences were observed between corresponding

Table 2 *Apnoea variables, per cent sleep, and respiration and heart rates in five infants during and after recovery from upper respiratory tract infection. Values are mean (SE)*

	Sleep phase	*During recovery*	*After recovery*
Apnoea index	Active	0·24 (0·07)	0·69 (0·42)
	Quiet	1·10 (0·46)	0·67 (0·18)
	Indeterminate	0·33 (0·20)	1·11 (0·49)
	Total	0·59 (0·24)	0·68 (0·23)
Apnoea attack rate	Active	0·04 (0·01)	0·09 (0·04)
	Quiet	0·14 (0·06)	0·08 (0·02)
	Indeterminate	0·06 (0·04)	0·15 (0·07)
	Total	0·08 (0·03)	0·13 (0·05)
Attack of longest duration (sec)	Active	5·20 (1·32)	6·20 (1·83)
	Quiet	5·84 (2·54)	7·68 (2·16)
	Indeterminate	2·80 (1·72)	4·62 (1·89)
	Total	7·22 (2·09)	7·78 (2·16)
Mean duration of attack of apnoea (sec)	Active	5·09 (1·28)	5·62 (1·53)
	Quiet	4·95 (2·14)	5·63 (1·72)
	Indeterminate	2·67 (1·63)	4·30 (1·76)
	Total	5·97 (1·62)	6·05 (1·60)
Apnoea per cent	Active	1·15 (0·36)	2·63 (1·31)
	Quiet	3·59 (1·58)	2·63 (0·70)
	Indeterminate	1·51 (0·93)	4·80 (2·09)
	Total	2·06 (0·79)	2·61 (0·76)
Sleep per cent	Active	42·20 (6·58)	39·80 (5·89)
	Quiet	41·80 (5·50)	52·40 (6·95)
Respiration rate	Active	38·25 (3·32)	36·95 (4·68)
	Quiet	32·04 (2·62)	34·20 (3·84)*
Heart rate	Active	132·00 (5·74)	134·90 (5·04)
	Quiet	127·74 (4·79)	131·32 (5·29)

*p<0·05.

Table 3 *Gross body movements and periodic breathing in relation to sleep phase in five infants during and after recovery from upper respiratory infection. Values are mean (SE)*

	Sleep phase	*During recovery*	*After recovery*
Body movements:			
Total duration (min/100 min sleep)	Active	5·68 (1·99)	1·48 (0·31)
	Quiet	0·68 (0·34)	0·63 (0·16)
	Indeterminate	58·21 (9·28)	39·10 (10·77)
	Total	12·80 (2·44)	4·01 (0·96)*
No/100 min sleep	Active	28 (10·18)	7 (1·59)
	Quiet	4 (2·13)	5 (1·88)
	Indeterminate	148 (14·87)	87 (14·11)
	Total	38 (6·71)	12 (2·46)*
Periodic breathing:			
Total duration (min/100 min sleep)	Active	0·38 (0·27)	1·31 (0·89)
	Quiet	1·22 (0·77)	0·83 (0·28)
	Indeterminate	0·59 (0·45)	0·58 (0·58)
	Total	0·75 (0·46)	1·12 (0·54)
No/100 min sleep	Active	1 (0·77)	4 (2·91)
	Quiet	3 (1·84)	3 (1·02)
	Indeterminate	2 (0·73)	2 (2·20)
	Total	2 (1·11)	4 (1·81)

*p<0·05.

variables in either active or quiet sleep. No infant had attacks of central apnoea exceeding 15 seconds. Three infants had brief (>3 and <6 seconds) or prolonged (>6 seconds) attacks of obstructive apnoea in active sleep during the course of infection, with resolution on clinical recovery. In no case did the maximum duration of an attack of obstructive apnoea exceed 10 seconds.

Table 3 gives the results for gross body movements and periodic breathing. The number and duration of movements for each 100 minutes of total sleep time was significantly increased during infection; no differences were observed in the amount of periodic breathing present.

Group 2: recurrent vomiting. Table 4 gives the results for apnoea variables, per cent sleep, respiration rate, and heart rate in relation to sleep state in the five infants during and after recovery from pyloric stenosis and in their matched controls without antecedent vomiting. Apnoea index, rate of attacks of apnoea, and apnoea per cent were significantly increased during illness, usually in both active and quite sleep states when compared with recovery or matched control data. Similarly, the mean and longest duration of attacks of apnoea were increased during illness. Two infants had prolonged (>15 seconds) attacks of central apnoea in both active sleep and quiet sleep (cases 1 and 5). The proportion of time spent in each sleep stage was comparable during and after illness. Respiration and heart rates were significantly lower in quiet sleep during illness than after recovery; respiration rate was reduced when compared with matched controls in both active and quiet sleep. Four infants with vomiting had prolonged (>6 seconds) attacks of obstructive apnoea in active sleep, with resolution on recovery. None of the matched control infants had either brief or prolonged attacks of obstructive apnoea.

Table 5 gives results for gross body movements and periodic breathing before and after recovery in index cases and also in matched control infants. The increase in body movements when symptoms were present did not reach significance when compared with controls, but the number of episodes and the total duration of periodic breathing were increased ($p=0·06$). Failure to reach significance in comparisons of index cases and controls is a reflection of the paucity of data available for non-parametric statistical comparisons. The Figure presents observations on periodic breathing in individual infants and illustrates the wide difference between illness and recovery data.

Table 4 *Apnoea variables, per cent sleep, and respiration and heart rates in relation to sleep phase in five infants with recurrent vomiting and their matched case controls. Values are mean (SE)*

	Sleep phase	*Infants with vomiting*		*Controls*
		During recovery	*After recovery*	
Apnoea index	Active	7·00 (2·48)	0·99 (0·52)*	0·67 (0·43)*
	Quiet	8·90 (5·17)	0·91 (0·45)*	0·65 (0·27)*
	Indeterminate	9·36 (4·23)	2·57 (0·96)*	0·69 (0·44)
	Total	7·56 (3·18)	1·13 (0·56)*	0·59 (0·26)*
Apnoea attack rate	Active	0·87 (0·29)	0·13 (0·07)*	0·08 (0·04)*
	Quiet	1·05 (0·62)	0·13 (0·06)*	0·08 (0·04)
	Indeterminate	1·05 (0·47)	0·31 (0·11)	0·09 (0·06)
	Total	0·90 (0·37)	0·15 (0·07)*	0·07 (0·03)*
Attack of longest duration (sec)	Active	13·30 (1·37)	7·38 (3·15)	6·38 (1·85)
	Quiet	13·02 (0·88)	7·88 (0·46)*	5·94 (2·59)*
	Indeterminate	9·14 (2·49)	8·04 (2·13)	4·18 (1·72)
	Total	14·82 (0·58)	9·66 (1·03)*	7·38 (2·12)*
Mean duration of apnoea (sec)	Active	7·95 (0·24)	7·33 (0·32)	5·78 (1·55)
	Quiet	9·48 (0·91)	7·03 (0·26)*	5·02 (2·13)
	Indeterminate	6·87 (1·75)	6·65 (1·67)	4·18 (1·72)
	Total	8·42 (0·18)	7·37 (0·29)	6·07 (1·61)
Apnoea per cent	Active	21·28 (6·34)	3·67 (1·83)*	2·41 (1·34)*
	Quiet	25·51 (14·22)	3·34 (1·42)*	2·29 (0·99)
	Indeterminate	27·36 (11·58)	8·91 (3·19)	2·86 (1·69)
	Total	22·14 (8·35)	4·08 (1·64)*	2·15 (0·81)*
Sleep per cent	Active	50·20 (2·63)	46·60 (2·50)	45·60 (5·49)
	Quiet	38·60 (5·07)	42·00 (3·70)	44·20 (6·76)
Respiration rate	Active	25·60 (1·11)	31·40 (2·70)	37·60 (3·00)*
	Quiet	22·50 (1·76)	27·20 (1·50)*	39·40 (4·12)*
Heart rate	Active	123·40 (6·63)	129·60 (5·94)	125·10 (8·00)
	Quiet	115·20 (5·73)	126·50 (4·58)*	120·70 (7·23)

*$p<0·05$.

Table 5 *Gross body movements and periodic breathing in relation to sleep phase in five infants during and after recovery from recurrent vomiting and their matched case controls. Values are mean (SE)*

	Sleep phase	*Infants with vomiting*		*Controls*
		During recovery	*After recovery*	
Body movements:				
Total duration (min/100 sleep)	Active	4·28 (0·83)	4·36 (0·52)	6·23 (2·32)
	Quiet	1·33 (0·45)	0·84 (0·32)	1·19 (0·56)
	Indeterminate	56·27 (11·34)	43·41 (3·92)	36·76 (11·57)
	Total	8·56 (2·20)	7·78 (1·77)	6·80 (1·25)
Number/100 min sleep	Active	24 (5·46)	25 (2·13)	24 (7·72)
	Quiet	11 (3·20)	5 (4·64)	12 (5·56)
	Indeterminate	275 (128·38)	120 (9·75)	77 (24·39)
	Total	35 (10·18)	29 (5·09)	23 (4·07)
Periodic breathing:				
Total duration (min/100 min sleep)	Active	18·91 (7·43)	1·93 (1·14)	0·62 (0·50)
	Quiet	21·28 (12·58)	0·84 (0·83)	0·56 (0·25)
	Indeterminate	12·41 (6·14)	1·46 (1·16)	0·00 (0·00)
	Total	15·65 (8·01)	1·31 (0·64)*	0·62 (0·25)
No/100 min sleep	Active	25 (7·06)	5 (2·40)	2 (1·19)
	Quiet	14 (8·46)	1 (1·00)	2 (0·85)
	Indeterminate	23 (10·12)	6 (4·49)	0 (0·00)
	Total	20 (7·48)	3 (1·26)*	2 (0·65)

*p=0·06.

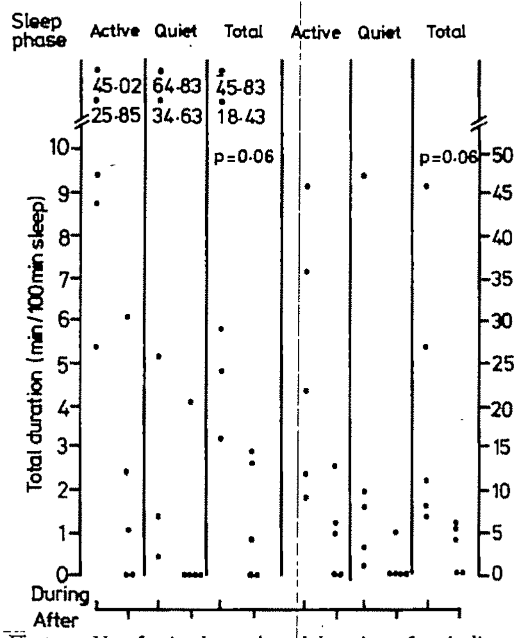

Figure *No of episodes and total duration of periodic breathing during sleep in five infants during and after recovery from recurrent vomiting.*

Discussion

These results present an opportunity to comment on the effects of natural stresses (upper respiratory infection and metabolic alkalosis) on breathing during sleep in infants, at an age when the incidence of sudden infant death syndrome is greatest.

An association between upper respiratory tract infection and sudden infant death syndrome is well documented by epidemiological and pathological studies.[5 14–17] Several authors have reported that prolonged attacks of apnoea occur more often during upper respiratory infection in infants thought to be at increased risk for the syndrome.[18–20] In the present study no differences were observed between indices of apnoea during and after recovery from infection. Prolonged attacks of central apnoea (>15 seconds) were not observed, but brief attacks of obstructive apnoea were present in three infants in active sleep, which scarcely affected heart rate. Obstructive attacks exceeding six seconds were accompanied by bradycardia. None of the full term infants studied was thought to be at increased risk for sudden infant death syndrome on epidemiological grounds.[21]

In view of the small number of cases studied it would be misleading to generalise on the likelihood of prolonged or severe attacks of apnoea in such cases. In a retrospective study of hospital charts of 274 infants under 6 months of age with proven respiratory syncytial virus infection Bruhn *et al* reported an association between respiratory infection caused by this virus and prolonged attacks of apnoea.[22] The association was strongest during the first months of life and in infants born prematurely. Mitchell *et al* reported a prospective study of the frequency and severity of attacks of apnoea in respiratory tract infections in infancy.[23] In nine infants with upper respiratory tract infection there were 121 attacks of apnoea exceeding 10 seconds (assessed by impedance pneumography), and in 8%

their duration exceeded 20 seconds. Severe bradycardia was sometimes unrelated to central apnoea. It is possible (perhaps probable) that these episodes of bradycardia resulted from attacks of obstructive apnoea not detectable by the methods they employed.

Gould *et al* described the effects of upper respiratory tract infection on twins studied polygraphically in the early months of life during two to three hour interfeed periods of sleep.[24] Infants with colds exhibited alterations specific for sleep state in sleep apnoea. At postconceptional ages of 40, 44, and 48 weeks the number of respiratory pauses of duration of 2·0 to 4·9 seconds and of 5·0 to 5·9 seconds for each 100 minutes of state were decreased during active and indeterminate sleep. This phenomenon did not occur at a postconceptional age of 52 weeks, suggesting that it had been modified by maturation. These authors hypothesised that the response described during the early weeks after birth was adaptive but for infants at risk for sudden infant death syndrome such adaptation could be overwhelmed, resulting in increased attacks of apnoea and sometimes sudden infant death. In our cases gross body movements were increased during the course of upper respiratory infection in relation to total sleep time (Table 3) and no differences were observed between infection and recovery values during quiet sleep. Thus arousals (as indicated by gross body movements) were increased generally and were unaffected during quiet sleep by upper respiratory infection.

In the infants with pyloric stenosis apnoea variables were significantly increased in both active and quiet sleep. Respiration and heart rates decreased in quiet sleep during the acute phase of illness when each infant had moderate metabolic alkalosis. Metabolic alkalosis of varying degree is nearly always present in such infants before surgical treatment.[25] In this situation the metabolic stimulus to breathing is reduced and any resulting abnormality in breathing pattern should be most obvious in quiet sleep.[26] Prolonged and potentially hazardous attacks of central apnoea might then result from loss of stimulus to wakefulness and/or a defect in metabolic control affecting central or peripheral chemoreceptor mechanisms. We observed prolonged attacks of central apnoea exceeding 15 seconds in two infants in both active and quiet sleep. In both infants gross body movements were increased during illness not only in relation to total sleep time but also quiet sleep, suggesting that arousal mechanisms were intact. Four of the five infants with pyloric stenosis also had attacks of obstructive apnoea during active sleep, perhaps due to loss of upper airway tone in that sleep state, possibly exaggerated by depletion of intracellular potassium. Prolonged attacks of either central apnoea or obstructive apnoea were not observed after clinical recovery or in the matched control infants. In a previous report we did not detect these abnormalities in 11 healthy infants free of symptoms with a mean age of 48·6 weeks (range 38–63 weeks) studied on 31 occasions in the early months of life.[27] Thus, despite the relative paucity of control data in the present study, it seems reasonable to ascribe our findings to the effects of 'minor' illness.

Whether infants exhibiting the breathing patterns observed in upper respiratory infection and pyloric stenosis are at increased risk for sudden infant death syndrome is not known. We have observed infants with upper respiratory infection, severe metabolic alkalosis, and congenital stridor presenting with 'near miss' for episodes of the syndrome, who exhibited in even greater degree the respiratory patterns described. One such infant presented with both upper respiratory tract infection and vomiting. Pyloric stenosis was suspected clinically and confirmed at operation. It is conceivable that the summation of such stresses, perhaps of minor significance individually, influences respiratory control to produce abnormalities of breathing patterns of sufficient severity in some infants to begin the sequence that culminates in a 'near miss' episode or even sudden death. It may be unnecessary to postulate a fundamental defect in respiratory or other control mechanisms in these circumstances. Our findings support the idea that infective and metabolic stresses, manifest as 'minor' illnesses in young infants, may have respiratory consequences that are potentially profound.

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Breast milk jaundice in premature infants

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SUMMARY In a randomised study of 186 preterm infants those fed on maternal or banked breast milk had a significantly higher peak bilirubin concentration and a more prolonged jaundice than infants fed an artificial preterm formula and were over four times more likely to achieve plasma bilirubin values above 200 μmol/l (11·7 mg/100 ml). This dietary effect was seen even in a high risk subgroup of sick ventilated infants below 1500 g who were receiving restricted enteral intakes. We suggest that breast milk jaundice in preterm infants may increase clinical intervention. Our findings are discussed in the light of epidemiological data suggesting an association between moderate hyperbilirubinaemia (>170 μmol/l) and neurodevelopmental outcome.

A small percentage of full term infants develop pronounced and prolonged breast milk jaundice. A more general tendency of breast fed infants to achieve higher plasma bilirubin concentrations than those fed with formula has been observed by some groups but not by others.[1] There have been few detailed longitudinal studies, however, on breast milk jaundice in infants born preterm; yet, as discussed below, a diet induced increase in plasma bilirubin concentration might be of greater clinical importance in this high risk subgroup than in the full term neonate. In this study we have examined the relation between diet, respiratory disease, birth weight, and plasma bilirubin concentrations in 186 infants born in one unit taking part in a larger, randomised multicentre dietary trial.

Subjects and methods

One hundred and eighty six preterm infants weighing less than 1850 g at birth, with a mean (SD) gestation of 31 (3) weeks and mean (SD) birth weight of 1385 (291) g, were studied.

Infants whose mothers elected not to provide their own milk were assigned randomly to receive either banked donor breast milk or a special preterm infant formula (Oster-Prem, Farley Health Products Ltd) as sole diets (primary trial). When mothers expressed their own 'preterm' milk the infants were assigned randomly to receive either banked breast milk or preterm formula as 'supplements' to their mother's milk in volumes according to the mother's success in expressing her milk (supplement trial). (The randomisation procedure is described in detail elsewhere.[2])

The median intake of maternal milk in the supplement trial was 46% of the total milk volume consumed.

Infants were studied until they reached a weight of 2000 g or were discharged from hospital. A blood sample, taken (for multiple purposes) at the time of routine clinical monitoring, was analysed for total plasma bilirubin concentration on the following mean (SD) days postpartum; 2(1), 5(1), 11(2), 18(2), 25(2), 34(3), and 50(7).

This study was designed to detect differences in bilirubin concentrations between randomised feed groups and not to derive 'normal' standards for plasma bilirubin in relation to diet. Our standardised blood sampling protocol would fail to detect the peak bilirubin value in some instances when this occurred on an intervening day (and thus our figures slightly underestimate maximum values in all feed groups).

Total plasma bilirubin was measured by the Jendrassik-Grof reaction, using a Roche kit in a centrifugal autoanalyser (Cobas Bio).

Ethical approval for the trial as a whole was obtained from the hospital ethical committees. Statistical analyses were performed using Student's *t* test, χ^2 test with Yates's correction, and Fisher's exact probability test.

Results

Details of the study population are shown in Table 1.

There was no difference between feed groups in mean gestation, birth weight, proportion receiving mechanical ventilation, or volume of intake of enteral feed during the first week. During the course of the study, the total number of subjects remaining in the study declined as follows: day 2, 186; day 5, 186; day 11, 182; day 18, 166; day 25, 140; day 34, 98; and day 50, 64. In the last period (34–50 days) there was a sharp fall in the proportion of subjects fed on the formula as a result of their faster growth rate on this diet and hence earlier discharge from hospital.

Figure 1 and Table 2 show that for each feed group the highest mean bilirubin concentration was seen at the second sampling period (day range 4–7, mean 5). At this age infants in the primary trial (Fig. 1) fed on banked breast milk had a significantly higher plasma bilirubin concentration than those fed on the preterm formula, 196 (SE 14) μmol/l (11·5 (0·8) mg/100 ml) compared with 147 (15) μmol/l (8·6 (0·9) mg/100 ml) ($p<0·02$). The subsequent decline in bilirubin concentrations was slower on banked breast milk: by a mean of 25 days, bilirubin concentrations were 76 (12) μmol/l on banked breast milk compared with 27 (7) μmol/l on the preterm formula ($p<0·001$). Also in the comparison of the supplement trial (Table 2), infants fed banked

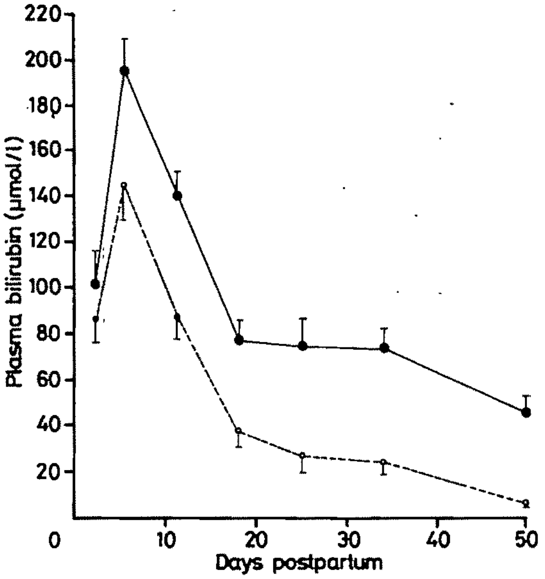

Fig. 1 *Change in total (SE) plasma bilirubin concentrations (μmol) with postnatal age in infants fed banked breast milk (●——●) compared with those fed a special preterm infant formula (○– – –○) as sole diets.*

Conversion: SI to traditional units—Bilirubin: 1 μmol/l ≈0·06 mg/100 ml.

Table 1 *Details of study population (n=186) classified by diet*

Diet	*Initial No of subjects entering study*	*Mean (SE) gestation (weeks)*	*Mean (SE) birth weight (g)*	*No of subjects ventilated*	*Total (SE) enteral feed volume/kg body weight during first week (ml)**
Primary trial:					
BBM	29	31 (0·6)	1409 (56)	15	628 (112)
PTF	30	31 (0·6)	1372 (55)	17	596 (87)
Supplement trial:					
EBM+BBM	62	31 (0·4)	1378 (36)	26	606 (53)
EBM+PTF	65	31 (0·4)	1388 (37)	29	597 (58)

BBM=Banked breast milk; PTF=preterm infant formula; EBM=expressed maternal breast milk.

Conversion: SI to traditional units—Bilirubin: 1 μmol/l≈0·06 mg/100 ml.

*Overall mean (SD) enteral feed volume during the first week in ventilated infants was 232 (27) ml and in non-ventilated infants was 917 (39) ml.

Table 2 *Comparison of mean (SE) plasma bilirubin concentrations (μmol/l) in infants fed on either banked breast milk (BBM) or preterm formula (PTF) as supplements to expressed maternal breast milk (median intake of maternal milk was 47% and 45%, respectively)*

Diets	*Days of age*						
	2	5	11	18	25	34	50
EBM+BBM (n=62)†	105 (10)	188 (9)*	139 (11)*	98 (10)	85 (12)*	44 (16)	16 (2)
EBM+PTF (n=65)	103 (10)	160 (11)	112 (8)	79 (10)	54 (7)	39 (5)	17 (2)

Conversion: SI to traditional units—Bilirubin: 1 μmol/l≈0·06 mg/100 ml.

*$p<0·05$.

†No of subjects entering study.

breast milk as a supplement to maternal expressed milk had higher concentrations of bilirubin on days 5, 11, and 25 than those seen when expressed maternal milk was supplemented with formula (p<0·05), though the difference was smaller than in the primary trial.

There was no influence of birth weight on 'peak' bilirubin concentration (which did not always occur at days 4–7 in individual infants). Infants who were mechanically ventilated, however, had higher overall mean peak bilirubin values compared with infants not requiring ventilation: 190(SE 7) *v* 151 (7) μmol/l (p<0·001). As very low birthweight infants who are sick possibly carry the greatest risk of bilirubin neurotoxicity we performed a preliminary analysis on peak plasma bilirubin of those infants with birth weight below 1500 g who had been randomly assigned to banked milk or formula as sole diets (primary trial). Figure 2 shows that in this subgroup infants who were ventilated had significantly higher mean peak bilirubin concentrations if they were fed on banked breast milk rather than preterm formula: 195 (18) μmol/l compared with 151 (11) μmol/l (p<0·05). The effect of diet in the non-ventilated group below 1500 g did not reach significance, though the population size was small (Fig. 2). The mean enteral feed volume intake in the first week in ventilated infants weighing less than 1500 g (primary trial) was only 195 (SE 52) ml compared with 822 (39) ml in the non-ventilated group (p<0·001); there was no difference in volume intake between diet groups in either case.

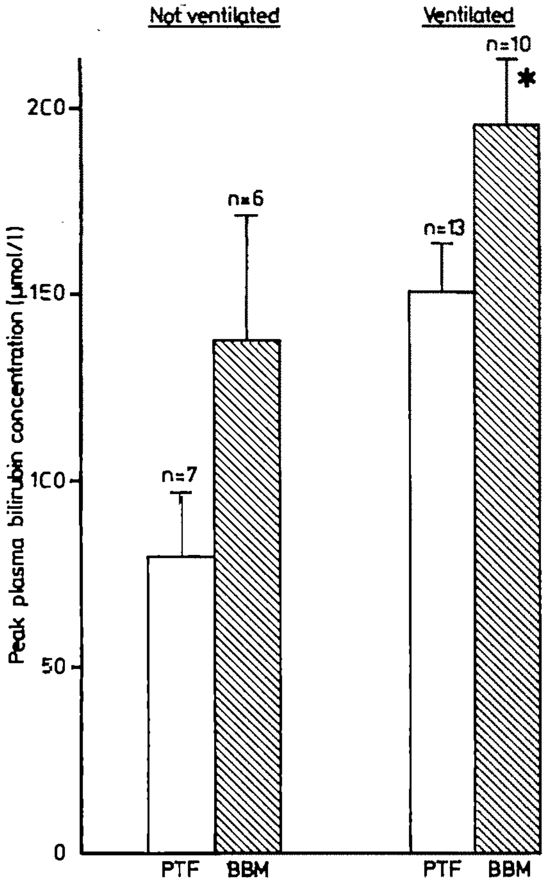

Fig. 2 *Effect of preterm formula (open columns) or banked breast milk (hatched columns) on highest recorded ('peak') (SE) bilirubin concentration (μmol/l) in infants with birth weight under 1500 g who were (right) and were not (left) mechanically ventilated.*

*p<0·05.

Conversion: SI to traditional units—Bilirubin: 1 μmol/l≈0·06 mg/100 ml.

In Figure 3 subjects of all birth weights are grouped according to their highest recorded (peak) bilirubin value and a non-randomised, epidemiological comparison is made between infants fed on

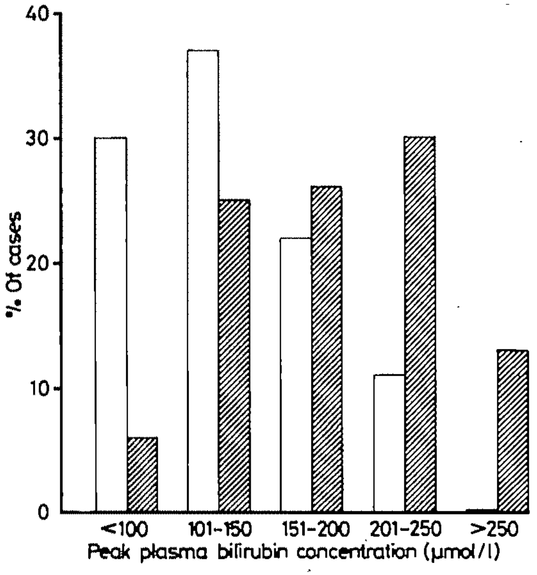

Fig. 3 *Percentage of subjects fed on preterm formula (n=30) (open columns) or human milk (banked breast milk or expressed maternal breast milk supplemented with banked breast milk, n=94) (hatched columns) grouped according to highest recorded ('peak') plasma bilirubin concentration (μmol/l).*

By χ^2, significantly higher proportion of formula fed infants with peak values <100 μmol/l and significantly lower proportion with values >200 μmol/l (p<0·01).

Conversion: SI to traditional units—Bilirubin: 1 μmol/l≈0·06 mg/100 ml.

formula alone and those fed on human milk (banked milk alone or expressed maternal milk supplemented, when required, with banked milk). Infants in the two groups fed human milk were combined as mean peak bilirubin values in each case were not significantly different. The proportion of infants whose highest recorded values did not exceed 100 µmol/l was significantly higher in the group fed formula (9/30:30%) than in the combined groups fed human milk (6/94:6%) ($\chi^2=9{\cdot}8$, $p<0{\cdot}01$). Conversely, a significantly higher proportion of infants fed human milk had their highest values over 200 µmol/l (40/94:43%) compared with the group fed preterm formula (3/30:10%) ($\chi^2=9{\cdot}3$, $p<0{\cdot}01$).

Discussion

In this randomised study preterm infants fed on human milk had higher peak concentrations of plasma bilirubin and more prolonged hyperbilirubinaemia than those fed on an artificial preterm infant formula. This dietary effect was apparent even with low feed volumes and was found in sick ventilated infants below 1500 g (Fig. 2) whose mean intake of banked breast milk or formula during the first week was only 200 ml.

A notable feature of a rise in plasma bilirubin concentration induced by breast milk, especially that seen with banked donor milk, is its persistence. Indeed, a major proportion of infants fed human milk who remained in hospital until 5–7 weeks postpartum were still frankly jaundiced (Fig. 1); some were investigated to exclude other causes. Although the number of infants at this analysis was too small to explore adequately an effect of diet on the need for either phototherapy or exchange transfusions, preliminary data suggest that both the use of phototherapy and the duration of its application tended to be greater in infants fed human milk than in those fed formula; this may have had the effect of reducing the potential difference in bilirubin concentrations between feed groups. The possibility that breast milk jaundice increases clinical intervention needs further exploration.

The most important question arising from our findings is whether or not diet induced hyperbilirubinaemia could have neurological sequelae. The neurotoxic effects of bilirubin are well established, yet the peak bilirubin concentration achieved by individual preterm infants has limited value for predicting neurological damage.[3] Thus while some infants may tolerate high concentrations of bilirubin without apparent consequences, others may develop frank kernicterus at low plasma bilirubin concentrations.[4–6] A number of factors have been identified that may influence bilirubin neurotoxicity; these include the binding of bilirubin to albumin or cells and the integrity of the blood-brain barrier, which may be affected in turn by asphyxia and acidosis.[7–10] Nevertheless, one large epidemiological study showed that for large populations there is an apparent, overall 'dose-response' relation between plasma bilirubin and motor delay.[11] The same study also showed an association between quite modest rises of plasma bilirubin—around 200 µmol/l—and such neurodevelopmental effects, especially in infants born preterm. Stewart reported that a bilirubin concentration of greater than 170 µmol/l was a significant factor associated with neurological handicap and sensorineural hearing loss in preterm infants.[12 13] Moreover, a variety of clinical and experimental studies have shown that the persistence of hyperbilirubinaemia may be a critical factor in determining the extent of neurological damage.[10 14] In the present study peak bilirubin values over 200 µmol/l (Fig. 3) were about four times more common in infants fed human milk (incidence 43%) than in those fed formula (incidence 10%).

Possibly the most vulnerable infants for bilirubin neurotoxicity are those of very low birth weight who have respiratory disease, which is commonly associated with low plasma albumin concentration and acidosis. It might be supposed that these infants would not be influenced by the type of milk chosen, as enteral intakes are usually limited in sick neonates. Yet our preliminary data show that even in this subgroup small volumes of human milk cause a significantly greater rise in plasma bilirubin than that seen with formula. Furthermore, we have shown that plasma bilirubin concentrations are higher in any case in infants with severe respiratory disease.

Despite these considerations, an epidemiological association between modest hyperbilirubinaemia and adverse neurodevelopmental effects does not imply necessarily a causal relation, and further work is needed in this area. The infants in this study represent a subgroup of over 900 babies from a multicentre feeding trial, and during their follow up (in progress) the relation between early diet, hyperbilirubinaemia, and subsequent neurological development is being examined. Given the information currently available, however, it might be unwise to disregard breast milk jaundice in high risk low birthweight infants. Temporary stopping of breast feeding (48 hours) has been used with success in full term infants with pronounced breast milk jaundice.[1] We speculate that brief stopping of human milk feeds might prove valuable in certain preterm infants, especially those who are sick, as an adjunct to other measures in the treatment and prophylaxis of hyperbilirubinaemia, though further investigation is required to explore the clinical consequences of such a manoeuvre.

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Dietary copper intake in artificially fed infants

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SUMMARY Plasma concentrations of copper and zinc and leucocyte concentrations of zinc were measured in mothers during later pregnancy, at delivery, and 8–10 weeks after birth, and plasma concentrations of copper and zinc were measured in their infants at delivery and 8–10 weeks after birth. The 145 infants were either breast fed or fed one of two milk formulas supplying copper at different concentrations. None of the infants achieved the minimum copper intakes recommended by the World Health Organisation (WHO). At 2 months of age there were no major differences in growth or health detected in infants fed the different copper intakes. Infant birth weight correlated well with the ratio of maternal venous plasma zinc:maternal leucocyte zinc at delivery. Maternal venous plasma copper and zinc concentrations at birth correlated with umbilical venous plasma copper and zinc concentrations. Infants fed the higher copper content formulas had a low mean plasma zinc concentration without a significant increase in the mean plasma copper concentration. The present WHO recommendations regarding minimum copper intakes for infants fed formulas cannot be achieved with currently available formulas and are probably wrong.

During 1979 a survey of 131 infants born in Glasgow was made to investigate their dietary intakes of lead, and it was found that most of the dietary lead ingested by bottle fed infants came from tap water.[1] Further analyses of a subsample, comprising 41 of the infants, showed that 37 (90%) had intakes of copper below the World Health Organisation (WHO)/Food and Agricultural Organisation recommended safe minimum intake of 1·26 µmol (80 µg)/kg body weight per day and 33 (80%) were below the recommended absolute minimum of 0·94 µmol (60 µg)/kg body weight per day. A smaller proportion of the zinc intakes were also below recommended concentrations. In view of this it was decided to give the initial priority to a study of copper intakes. The purpose of the investigation now described was to examine the plasma concentrations of copper in the mothers during later pregnancy, at delivery, and 8–10 weeks later, and in the infants at delivery and 8–10 weeks after birth. These infants were either breast fed or fed one of two milk formulas supplying copper at different concentrations, one at the upper end of the range of normal concentration and the other at the lower end of the range. The relation between the type of milk and growth and the effect of the type of milk on the concentrations of plasma copper and zinc are examined.

Patients and methods

Mothers and infants. Mothers attending prenatal clinics in a large housing scheme and in the Queen Mother's Maternity Hospital, Glasgow, volunteered to take part after a full explanation of the aims of the study.

One hundred and four infants born at term with a normal birth weight (>2500 g) and 41 low birthweight (<2500 g) infants completed the study. Infants within each group were randomly allocated to a 'low copper' or 'high copper' formula except when the mother chose to breast feed her infant. These data, gender, birth weights, gestational ages, and feeding groups are shown in Table 1. The gestational age range of the low birthweight infants was 32–40 weeks. The birth weights of seven low birthweight infants lay between the 10th and 20th

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*For the Glasgow Copper Intake Study Group: TS Wilson, (chairman), JC Sherlock (director of study). Members: G Chittick, HT McIntosh, R Paterson, AP Robertson, S Salim, A Vardag, W Daoud, GI Forbes, A Green, W Richards, GC Arneil, F Cockburn, RW Logan, RT Leslie, EM Gibb, MM Miller, J Scott, J Farquharson, F MacMillan, J Warren, A Burrell, S Davis.

Table 1 *Clinical details of groups of low (<2500 g) and normal (> 2500 g) birthweight infants fed human milk or high or low copper milk formula*

	Sex	*Group*								
		Breast fed			*Low copper*			*High copper*		
		n	*Mean (SD)*	*Range*	*n*	*Mean (SD)*	*Range*	*n*	*Mean (SD)*	*Range*
Normal birthweight infants										
Birth weight (g)	M	14	3885 (593)	3240–5000	23	3494 (388)	2800–4380	14	3522 (325)	2910–4120
	F	20	3511 (361)	2610–4280	18	3340 (371)	2560–4220	15	3550 (457)	2900–4700
Gestation (wks)	M	14	40·5 (0·8)	40–42	23	40·0 (0·8)	38–41	14	39·9 (1·0)	37–42
	F	20	39·8 (0·8)	38–41	18	39·8 (0·9)	37–41	15	40·1 (0·5)	39–42
Low birthweight infants										
Birth weight (g)	M	4	2145 (488)	1800–2499	6	2054 (455)	1430–2460	10	2246 (182)	1940–2490
	F	4	2250 (195)	1970–2450	10	2228 (293)	1550–2490	7	2152 (371)	1490–2499
Gestation (wks)	M	4	38·5 (2·4)	35–40	6	35·9 (2·5)	33–40	10	36.6 (2·0)	33–40
	F	4	36·8 (3·4)	32–40	10	36·8 (2·5)	33–40	7	37·3 (2·9)	33–40

centiles for Scottish infants,[2] and the remaining 34 were below the 10th centile.

Of the three boys in the group between the 10th and 20 centiles, two were in the high copper group and one in the low copper group. Of the four girls in this centile group, one was in the high copper group, two in the low copper group, and one was breast fed. None of the infants required assisted ventilation or suffered appreciable neonatal disease that might have interfered with early weight gain. From birth onwards the infants were fed on demand until satisfied.

During a period of seven days preceding the 8–10 week blood samples, the mother kept a diary recording the volumes of infant formula consumed during each day. The postconceptional ages during which the dietary intakes were recorded ranged from 40 to 49 weeks (median 47·8 weeks) and the postnatal ages from 8 to 10 weeks (median 9·2 weeks).

Milks. The low copper milk was an Ostermilk Complete Formula (Farley Health Products) in standard use until 1983, containing 0·5 µmol/l (3 µg/100 ml) of copper. The high copper milk was the same basic formula but with a copper content of 6·3 µmol/l (40 µg/100 ml), which has been available since 1983.

The zinc concentration in both formulas was 78 µmol/l (510 µg/100 ml). Analysis of the mature human milk obtained by manual expression at 6 to 9 weeks from mothers of 29 normal birthweight and seven low birthweight infants gave a mean copper concentration of 5·8 µmol/l (37 µg/100 ml) and a mean zinc concentration of 27·1 µmol/l (177 µg/100 ml).

Samples for analyses. Venous blood samples were obtained from mothers at 28 weeks' gestation, at the birth of the infant, and at 8–10 weeks after the birth. A heel prick blood sample was obtained from the infant 8–10 weeks after birth. Where practicable, samples of cord blood and amniotic fluid were also collected. Blood samples were analysed for plasma copper and plasma and leucocyte zinc concentrations. Infant hair was obtained at 8–10 weeks for determination of copper content. Amniotic fluid was centrifuged immediately after collection and the supernatant later analysed for total copper and total zinc concentrations.

Biochemical analysis. Plasma copper and zinc analyses were performed using atomic absorption equipment by the procedure detailed in a previous publication.[3]

In the case of copper, within and between batch coefficients of variation at a plasma concentration of 3·4 µmol/l were 8·6% and 10%, respectively. At a concentration of 13·4 µmol/l the corresponding figures were 2·9% and 3·5%. The sensitivity of the method for 95% confidence limits was 0·3 µmol/l. In the case of zinc, the intrabatch and interbatch coefficients of variation were 9·8% and 11·4% at 4·4 µmol/l and 3% and 3·8% at 19·2 µmol/l, and sensitivity of the method was 0·5 µmol/l.

For measurements of both copper and zinc, quality control was effected by incorporating specimens from the Guildford quality control scheme in each batch of assays. No analysis was accepted where the result for control serum samples differed by more than one standard deviation from the mean.

Whole blood was employed for measurement of lead. Preparation of leucocyte pellets for determination of zinc was undertaken, using lithium heparinised venous whole blood, dextran separation of leucocytes, centrifugation, and repeated washing. The protein determination was by the Lowry technique.

Analysis of hair copper was by atomic absorption spectrophotometry, which was also employed for the determination of the copper and zinc concentrations in breast milk and amniotic fluid.

Growth measurements. Accurate measurements of weight, length, arm circumference, occipitofrontal circumference, and subscapular and triceps skinfold thicknesses were obtained at birth and at 8–10 weeks after birth. Crown-heel length was measured using a Holtain neonatometer, infants were weighed on standard beam scales, occipitofrontal circumferences and mid-arm circumferences were measured to the succeeding millimetre using a paper tape, and skinfold thicknesses were measured using Holtain callipers (British Indicators Ltd).

Results

Infants of low birth weight and on the low copper diet ingested 0·08 μmol (4·9 μg)/kg body weight per day of copper, while those on the high copper diet ingested 1·02 μmol (65 μg)/kg body weight per day. In the normal birthweight infants the corresponding values for those fed the low and high copper diets were 0·07 μmol (4·4 μg)/kg body weight per day and 0·92 μmol (58 μg)/kg body weight per day.

Breast milk analyses showed that the breast fed infants took in 0·58 μmol (37 μg) of copper and 2·71 μmol (177 μg) of zinc for every 100 ml ingested, giving a copper:zinc ratio in the breast fed infants diet of 0·21. The copper:zinc ratio for infants fed low copper formula was 0·006 and for those fed the high copper formula was 0·08.

Concentrations of copper and zinc in the venous blood plasma from the mothers at 28 weeks' gestation, at birth, and at 8–10 weeks after birth, together with concentrations in the umbilical venous plasma and infant capillary plasma at 8–10 weeks after birth are shown in Table 2. There was no significant correlation between copper or zinc concentrations measured in the three maternal plasma samples. There was a significant correlation between copper concentrations in maternal plasma taken at the time of birth and in the umbilical venous plasma. Zinc concentrations showed a similar correlation. The appropriate values for plasma copper concentrations were $r=0\cdot31$ and $p<0\cdot001$ and for plasma zinc concentrations were $r=0\cdot17$ and $p<0\cdot001$.

The mean plasma zinc concentrations in maternal blood were not significantly different between 28 weeks' gestation and delivery but increased significantly after the birth of the infant. Similarly, the mean plasma copper concentration in maternal blood at 28 weeks' gestation and at birth were not significantly different, but after birth the concentrations fell to normal values. Concentrations of copper and zinc in the infant's plasma 8–10 weeks after birth did not correlate with any of the other measurements of copper and zinc.

Amniotic fluid copper concentrations obtained from six low birthweight infant deliveries ranged from 1·6 to 16·5 (mean (SD) −8·5 (6·3)) μmol/l and zinc from 1·5 to 14·2 (7·3 (4·7)) μmol/l. Values for copper obtained from amniotic fluid samples from 24 normal birthweight infants ranged from 0·5 to 14·0 (3·2 (3·7)) μmol/l and for zinc from 0·3 to 30·6 (8·6 (9·0)) μmol/l.

All plasma copper and zinc concentrations displayed essentially normal distributions. In the case of amniotic fluid, copper and zinc concentrations and leucocyte zinc concentrations log-normal distributions obtained.

Table 2 *Concentrations of zinc and copper in maternal venous blood plasma at 28 weeks' gestation, at birth, and at 8–10 weeks after birth, infant umbilical venous blood, and infant capillary blood at 8–10 weeks after birth in low (<2500 g) and normal (> 2500 g) birthweight infants*

Plasma samples	*Zinc (μmol/l)*						*Copper (μmol/l)*					
	Low birthweight			*Normal birthweight*			*Low birthweight*			*Normal birthweight*		
	n	*Mean*	*(SD)*	*n*	*Mean*	*(SD)*	*n*	*Mean*	*(SD)*	*n*	*Mean*	*(SD)*
Maternal:												
At 28 weeks' gestation	22	13·7	(2·8)*	99	12·0	(3·2)*	11	30·5	(8·7)	101	30·5	(6·0)
At birth	12	13·5	(2·8)*	89	11·1	(3·2)*	23	34·2	(8·5)	89	31·2	(7·9)
At 8–10 weeks after birth	30	16·8	(3·0)*	96	15·3	(3·1)*	32	20·5	(7·9)	97	20·5	(6·1)
Umbilical venous blood	24	20·8	(3·8)*	72	18·8	(4·9)*	32	6·9	(3·6)	75	6·9	(2·5)
Infant capillary blood at 8–10 weeks after birth	30	16·1	(4·6)	83	15·5	(5·5)	32	11·6	(4·7)	95	11·8	(3·0)

*Difference between pairs of means significant at $p<0\cdot05$.

Table 3 shows plasma and leucocyte zinc concentrations in mothers before, at, and after delivery and in the infants at delivery in low birthweight and normal birthweight groups. When the ratios of plasma zinc:leucocyte zinc in maternal blood at delivery were examined in relation to infant birth weight there was a significant negative correlation ($r=-0·38$; y (ratio)$=2·86-0·47\times$(birth weight), $n=68$).

Comparison of values in low and normal birth weight infants. There were no significant differences between the mean copper concentrations in the blood of mothers having low and normal birthweight infants at any of the sampling times. Similarly, there were no significant differences in the umbilical venous plasma copper concentrations or in the infants' plasma concentrations at 8–10 weeks. There was no difference in the mean plasma zinc concentrations for low and normal birthweight infants at 8–10 weeks. There were significant differences in the mean plasma zinc concentrations between the mothers of low and normal birthweight infants at 28 weeks' gestation, at delivery, and at 8–10 weeks after birth; in each instance the higher zinc concentrations were in the low birthweight group. The umbilical venous plasma zinc concentrations were significantly higher in the low birthweight than in the normal birthweight infants.

Considering the four pairs of means together and bearing in mind that the serial zinc concentrations are not correlated, the results indicate that mothers

Table 3 *Zinc concentrations in maternal venous plasma (μmol/l) and leucocytes (mg/kg protein) at 28 weeks' gestation, at delivery, and 8–10 weeks after delivery in mothers of low (<2500 g) and normal (>2500 g) birthweight infants and in infant umbilical venous blood*

	Blood sample	*Low birthweight*				*Normal birthweight*			
		n	*Mean*	*(SD)*	*Range*	*n*	*Mean*	*(SD)*	*Range*
Maternal blood:									
At 28 weeks' gestation	Plasma	22	13·7*	(2·8)	8·6–19·7	99	12·0*	(3·2)	2·3–23·3
	Leucocyte	4	61·2	(30·4)	35–90	68	107·0	(45·2)	40–275
At delivery	Plasma	12	13·5*	(2·8)	6·7–17·0	89	11·1*	(3·1)	0·92–19·4
	Leucocyte	17	58·8	(32·8)	25–145	68	72·8	(31·7)	20–210
At 8–10 weeks after delivery	Plasma	30	16·8*	(3·0)	11·3–24·8	96	15·3*	(3·1)	4·3–29·4
	Leucocyte	26	135·0	(64·8)	60–335	67	171·0	(71·5)	50–380
Infant umbilical venous blood at delivery	Plasma	24	20·8*	(3·8)	11·8–25·7	72	18·8*	(4·9)	9·2–32·0
	Leucocyte	6	168·0	(39·8)	120–240	27	116·0	(55·0)	45–245

*Difference between pairs of means significant at $p<0·05$.

Table 4 *Concentrations of copper and zinc (μmol/l) in maternal venous blood plasma at 28 weeks' gestation, at birth, and at 8–10 weeks after birth and in infant umbilical venous blood and capillary blood at 8–10 weeks after birth related to feeding group*

Blood sample		*Feeding group*								
		Breast			*Low copper*			*High copper*		
		n	*Mean*	*(SD)*	*n*	*Mean*	*(SD)*	*n*	*Mean*	*(SD)*
Maternal blood:										
At 28 weeks' gestation	Copper	30	28·3	(6·8)	38	31·5	(6·6)	30	30·2	(5·7)
	Zinc	36	12·7	(3·7)	39	11·9	(3·5)	31	12·2	(2·3)
At delivery	Copper	33	29·9	(8·2)	34	32·9	(9·6)	32	31·8	(6·5)
	Zinc	28	11·0	(3·7)	31	10·7	(3·2)	28	12·4	(3·1)
At 8–10 weeks after delivery	Copper	35	17·5	(3·6)	41	21·7	(6·9)	35	20·9	(7·4)
	Zinc	34	15·6	(3·5)	40	15·8	(3·7)	35	15·3	(2·4)
Umbilical venous blood	Copper	30	6·9	(3·1)	36	6·6	(3·0)	28	7·2	(2·8)
	Zinc	28	18·8	(5·5)	31	18·7	(4·6)	25	19·7	(3·8)
Infant's blood at 8–10 weeks after birth	Copper	35	12·4	(3·5)	41	11·2	(3·1)	33	11·8	(4·2)
	Zinc	30	17·6	(5·8)*	38	15·8	(4·7)	30	13·8	(4·3)*

*Difference between means significant at $p<0·005$.

who have low birthweight infants tend to have higher plasma zinc concentrations than those who have normal birthweight infants.

Effect of the feeding regimen. There were no significant differences in umbilical venous plasma copper concentrations between low and normal birthweight infants; consequently, the data for these two groups have been combined when comparing the plasma copper concentrations obtained from infants on the three feeding regimens (Table 4).

Mothers who breast fed their infants tended to have lower plasma copper concentrations than the other mothers; the differences, however, between the mean concentrations at 28 weeks' gestation, at birth, and at 8–10 weeks after birth were not significant. The mean umbilical venous plasma copper concentrations were almost identical for the three groups of infants. Breast fed infants aged 8–10 weeks had the highest mean plasma copper concentration, the infants in the low copper group the lowest, and the infants in the high copper group an intermediate value. The difference between the mean plasma copper concentration for the infants who were breast fed and the infants in the low copper group did not reach significance at the 5% level (p=0·086). The plasma zinc concentrations in the breast fed infants were also greater than the values found in the formula fed infants, and it is noticeable that the lowest mean plasma zinc concentration was found in the infants in the high copper group (p=<0·005) (Table 4).

Table 5 *Copper:zinc concentration (molar ratios) in diets and in plasma of infants after 8 weeks being breast fed or fed on a high or low copper content milk*

Feeding group	*Copper:zinc ratio*	
	Diet	*Plasma*
Breast fed	0·21	0·70
Low copper formula	0·006	0·71
High copper formula	0·08	0·86

The mean plasma copper:zinc ratios were similar despite wide differences in the dietary ratios of copper and zinc in the three feeding regimens. Table 5 gives the increments between birth and 8 weeks in the low and normal birthweight infants fed their mother's breast milk or high or low copper content formulas.

Infant growth. Rates of growth of the infants during the first eight weeks after birth were calculated as the arithmetic difference of their measurements taken at birth and at 8 weeks; rates of growth were ascertained for each of the six measurements weight, length, head circumference, arm circumference, and triceps and subscapular skinfold thicknesses (Table 6).

Analyses of variance were carried out for normal

Table 6 *Growth increments between birth and 8 weeks in low (<2500 g) and normal (> 2500 g) birthweight infants fed low or high copper content formulas or human milk*

	Feed	*Low birthweight*			*Normal birthweight*		
		n	*Increment*	*SD (pooled)*	*n*	*Increment*	*SD (pooled)*
Weight (kg)	BF	8	1·861		33	1·900	
	LC	16	1·831	0·387	38	1·806	0·555
	HC	15	1·925		28	1·656	
Length (cm)	BF	8	7·98		33	8·02	
	LC	16	9·46	2·11	38	8·68	1·79
	HC	15	9·07		28	8·87	
Occipitofrontal circumference (cm)	BF	8	5·388		33	4·741	
	LC	16	6·112	1·104	38	4·689	1·091
	HC	15	5·707		28	4·654	
Arm circumference (cm)	BF	8	2·413		33	1·657	
	LC	16	2·881	1·050	38	1·454	1·097
	HC	15	3·153		28	1·129	
Triceps skinfold (mm)	BF	8	3·475		33	3·794	
	LC	16	3·781	1·611	38	2·921	1·748
	HC	15	3·433		28	2·268	
Subscapular skinfold (mm)	BF	8	3·500		33	3·152	
	LC	16	3·462	1·276	38	2·487	1·770
	HC	15	2·640		28	2·121	

BF=Breast fed; LC=low copper formula; HC=high copper formula.

and low birthweight categories and for each of the six measurements in each of the three feed categories. No consistent dietary effect was found except for a greater increase in triceps skinfold thickness in normal birthweight breast fed infants (mean increase in triceps skinfold thickness for infants who were breast fed was 3·8 mm, for infants in the low copper group was 2·9 mm, and for infants in the high copper group was 2·3 mm). The triceps skinfold thicknesses of the infants fed the high and low copper content formulas did not differ significantly from each other. The difference between the breast fed and formula fed infants was significant at a 1% level. Despite this, the difference may be unremarkable; with so many comparisons being made it is not surprising that one of them achieved significance.

A series of 20 tables giving fuller information about infant growth characteristics as well as the full results of biochemical analyses of concentrations of maternal and infant plasma copper and zinc, maternal and umbilical venous leucocyte zinc, blood lead, amniotic fluid copper and zinc, breast milk copper and zinc, and infant's hair copper at 8 weeks can be obtained.*

Discussion

The dietary requirement of the fetus for copper must be met from the maternal diet and maternal tissue reserves, and in turn this might influence the copper reserves in the preterm or term newborn. Bioavailability of copper depends on various factors, including concentrations and distribution of copper binding and carrying proteins and concentrations of other dietary constituents, including phytate and zinc.

Sturgeon and Brubaker described the typical clinical features of copper deficiency in infancy in 1956,[4] and Al-Rashid and Spangler described an infant of low birth weight who developed oedema, anaemia, bone disease, and recurrent apnoea associated with a low plasma copper concentration in 1971.[5] Both studies showed that these abnormalities could be corrected by giving copper supplements. Since then numerous reports of isolated copper deficiency in infants have been published.[3 6–8] Copper deficiency in preterm low birthweight infants has already been reported from Glasgow and a previous dietary survey showed very low copper intakes during infancy.

In the present study there was no obvious problem shown during the first eight weeks of life related to a copper intake of 0·5 µmol/l of formula compared with an intake of 6·3 µmol/l, even in low birthweight infants.

Fetal copper metabolism differs substantially from that of the older infant and child. At birth the liver copper concentrations are five to 10 times greater than in the adult,[9] but in spite of this the plasma concentrations of copper and the copper carrying caeruloplasmin are much lower than in the older infant and child. In fetal and neonatal liver biopsy specimens the excess copper can be shown histochemically, as can a copper associated protein not demonstrable in the more mature liver.[10] This copper can be located within electron dense lysosomes with a specific neonatal carrier protein believed to be localised to lysosomes rather than mitochondria.[11] Although the liver copper concentrations are within the range associated with homozygous Wilson's disease, there is no biochemical, structural, or ultrastructural evidence of copper toxicity and the copper is complexed and packaged in membrane bound lysosomes.[10] At about 3–4 months of age both liver copper and plasma concentrations of copper and caeruloplasmin approach the adult range.[12]

Sutton *et al* showed that poor growth, peripheral oedema, osteoporosis, neutropenia, anaemia, and apnoea can occur in copper deficient infants with birth weights less than 1500 g.[3] At such very low birth weights reserves of liver copper are minimal and it is not surprising that dietary deficiencies can result in clinical abnormalities. In the older infants in this study, irrespective of birth weight, there was no evidence of clinical abnormality or disturbance in growth, even though the highest copper intake was still below the WHO minimum recommended intake.

Mean haemoglobin concentrations and packed cell volumes at 8–10 weeks of age were not significantly different between the six groups of infants in this study. Evidently, copper reserves and copper intakes were adequate to maintain haemoglobin synthesis in spite of intakes below the recommended minimum.

Whether there will be long term effects on body tissues from such low copper intakes is unknown. Copper is present in many intracellular enzymes, and reduced function of these in the copper deficient state may interfere with collagen synthesis through a deficiency of lysyl oxidase activity and poor quality elastin. The function of the copper dependent superoxide group of enzymes is to protect the cell from the superoxide radical, and failure of antioxidant mechanisms has been reputed to increase the rate at which tissues age.

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Although the dietary ratios of copper and zinc in the breast fed infants and infants in the low copper group were very different, mean plasma copper:zinc ratios were similar. Infants fed high copper formula had a greater mean plasma copper:zinc ratio than breast fed infants or infants fed low copper formula. Copper and zinc are biological antagonists, and dietary supplementation with zinc in man reduces the copper:zinc ratio in plasma.[13 14] In rats reduced copper:zinc ratios were associated with hypercholesterolaemia,[15] but recent workers have failed to confirm this.[16]

Influence of maternal intakes of copper and zinc during pregnancy on the growth rates of the fetus have been examined.[17–21] There was no obvious correlation between the amniotic fluid copper and zinc concentrations and infant birth weight or gestational age.

The maternal plasma copper and zinc concentrations and maternal white blood cell zinc concentrations in this study also failed to show any direct correlation with infant birth weight. Mean white cell zinc concentration in mothers with light for dates, growth retarded infants was lower than in mothers of appropriately grown preterm and term normal birthweight infants, but these differences failed to reach significance. This might reflect the small numbers studied.

The data indicate that ratios of maternal venous plasma zinc to leucocyte zinc at delivery are related to infant birth weight. Further investigation of the association of a fairly high plasma and low leucocyte zinc as a possible index of maternal zinc deficiency and impaired fetal growth is warranted.

Dietary zinc deficiency has been postulated in young women who are not pregnant in West Scotland.[22] The present study did not examine maternal intake but confirms the high plasma zinc concentrations reported in mothers of low birthweight infants during pregnancy.[23 24] No overt pre-eclampsia occurred in our mothers of low birthweight infants. These same mothers had lower mean white blood cell zinc concentrations than mothers of normal birthweight infants at 28 weeks' gestation, at delivery, and at two months post partum. This might be explained by a relative reduction in zinc binding substances within leucocytes and an increase in plasma zinc binders in the blood of mothers of low birthweight infants but cannot be explained on the basis of plasma volume differences[20] or free zinc concentrations.[25] These important findings clearly justify further investigation into the role of zinc in fetal and infant development.

The infants studied had copper intakes below the minimum WHO recommendations without obvious physical or biochemical problems at the age of 2 months. With present milk formulas it is unlikely that WHO minimum recommendations for copper intake can be achieved. Either there is a subclinical copper deficiency state in infants or the WHO recommendations are in error. If manufacturers increase only the copper content in their formulas to achieve the WHO recommendations this could critically reduce the bioavailability of zinc in their formulas. Although the infants in this study were all healthy, infection or other illness might precipitate a problem associated with 'borderline' copper intakes.

The extraordinary adaptability of the human newborn infant to wide variation in copper intake and in copper:zinc ratio intake is noted. Whether there is any long term consequence of such adaptation remains to be proved.

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Respiratory distress syndrome and inositol supplementation in preterm infants

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SUMMARY We report a randomised double blind trial of *myo*-inositol (inositol) supplementation for 10 days in 74 preterm infants with a birth weight less than 2000 g (mean gestational age 29·5 weeks and mean birth weight 1266 g). All infants required artificial ventilation for treatment of respiratory distress syndrome. Inositol (120–160 mg/kg/day) was administered by the ingastric or intravenous route. The 37 infants who received inositol supplementation required less mechanical ventilation during days 4–10, had less failures of indomethacin to close ductus arteriosus, and had less deaths or bronchopulmonary dysplasia, or both, than the infants treated with placebo. There were no detectable adverse effects. These preliminary results suggest that inositol is an important nutrient in immature preterm infants.

Myo-inositol (inositol), a six carbon sugar alcohol, is at least as abundant as glucose in the body. In adults virtually all inositol is intracellular, whereas fetuses and immature preterm infants may also have high concentrations of inositol in serum.[1–3] Inositol is a precursor of phosphoinositides. These phospholipids are membrane components and may serve, for instance, as a putative neurotransmitter, as 'tertiary' messengers of several hormones, and as a growth factor.[4] Although rodents on an inositol deficient diet may develop skin,[5] gastrointestinal,[6] and hepatic[7] disturbances, dietary inositol requirements have not been established.[8] The observation that inositol is synthesised in any tissue and is taken up into intracellular space by active transport has led to a limited nutritional interest in this compound.

Recently, it was found that an excess of inositol potentiates the glucocorticoid induced acceleration of the differentiation of lung surfactant.[9] As critically ill newborn are deprived of breast milk rich in inositol, resulting in a decrease in serum inositol,[3–10] it was prudent to test whether exogenous inositol influenced the respiratory course in severe respiratory distress syndrome (RDS). The rationale of the study was to provide an intake of inositol similar to that in full breast feedings. The present report deals with a randomised double blind pilot study that evaluates the influence of inositol in treatment of RDS.

Patients and methods

Clinical methods.

Study population

The study was conducted in our hospital between January 1983 and August 1985. Preterm infants had to fulfil the following criteria to be included in the study:

1. Birth weight <2000 g.
2. Diagnosis of RDS.
3. Mechanical ventilation required for a period of at least 24–48 hours.
4. No other cardiopulmonary disease, malformation, or sepsis at birth or fetal hydrops.

RDS was diagnosed on the basis of the following criteria:

1. Symptoms and findings of respiratory distress (tachypnoea, retractions, grunting, apnoea, or extra oxygen required) for at least 72 hours from birth.
2. Chest *x* ray film compatible with RDS.[11]
3. Low lecithin:sphingomyelin ratio and undetectable phosphatidylglycerol in tracheal aspirate during the first 24 hours.

The lung effluent was obtained shortly after intubation during routine suctioning of the airways. Normal saline (1–2 ml) was injected through the endotracheal tube. After a short hand ventilation any fluid that was recovered during suctioning of the airways (1 cm distal to the tip of the endotracheal tube) was collected into a Leuken's trap. The phospholipids were analysed using two dimensional thin layer chromatography.[12]

Administration of sugars

Infants were randomly and blindly assigned to be treated with inositol or placebo (glucose) after their parents had consented to their participation. Each set of solutions, containing either inositol or glucose (5% weight/volume each) had a code number. Only the pharmacist preparing the doses knew the contents of the drug packages. The sugars were given intragastrically shortly before gavage feedings in a dose of 160 mg/kg/day, divided into four doses. When all oral feeds were withheld the sugars were given intravenously. Based on a study of bioavailability (manuscript in preparation) the intravenous dose given was 75% of the intragastric one. All sugars were stored at −20°C and were discarded with 24 hours of use. The sugars were started at 12–48 hours of age and continued until 10 days. Contraindications for entry into the trial and indications for stopping the administration of sugars were low urine output (<1 ml/kg/h) or raised blood urea concentrations (>8·3 mmol/l (50 mg/100 ml)), or both.

General management of infants

The indications for intubation and ventilation were apnoea at birth that did not respond to mask ventilation, requirement of >60% oxygen, or failure to maintain arterial carbon dioxide tension below 70 mm Hg. Assisted ventilation was provided by a Baby Bird infant ventilator, using intermittent mandatory ventilation or continuous positive airway pressure. In general initial ventilator rates were 20–40/min, inspiratory time 0·8–1·0 seconds, peak inspiratory pressure 15–20 cm H_2O, and positive end expiratory pressure 2–5 cm H_2O. Peak inspiratory pressure was increased when fractional inspiratory oxygen requirements were higher than 0·8. Occasionally, when the conventional technique failed, infants were ventilated at a rate of 50–70/min. When the fractional inspiratory oxygen required was below 0·8, peak inspiratory pressure and ventilator rate were decreased. Small preterm infants were extubated when they required fractional inspiratory oxygen <0·3, positive end expiratory pressure <3 cm H_2O, and ventilator rates <4/min, whereas infants weighing >1500 g were given continuous positive airway pressure before extubation. Apnoea of prematurity was treated with theophylline.

All infants had transcutaneous oxygen monitoring when fractional inspiratory oxygen was >0·3. Arterial oxygen tension was monitored from the abdominal aorta or radial artery. The ventilator settings and oxygen concentrations were adjusted frequently to maintain an oxygen tension or transcutaneous oxygen tension between 50 and 70 mm Hg and carbon dioxide tension between 40 and 60 mm Hg. Blood pressure was measured by Doppler ultrasound method. Infusions of 4% albumin or fresh frozen plasma (10–20 ml/kg) and dopamine (initial dose of 2–5 μg/kg/min) were given if the systolic blood pressure was below 45–50 mm Hg.

Patent ductus arteriosus was suspected if there was an enlarged cardiac silhouette and pulmonary vascular plethora on the chest *x* ray film, increase in pulse pressure, increase in retention of carbon dioxide, or metabolic acidosis, even in the absence of a heart murmur. Patent ductus arteriosus was confirmed by echocardiography. Intravenous indomethacin was given (0·2 mg/kg as an initial dose and then 0·1 mg/kg at 12 and 24 hours) in the absence of contraindications (low platelets or active bleeding). If closure was not evident within 48–72 hours as assessed by sequential echocardiography the patent ductus arteriosus was surgically ligated.

Mean airway pressure, when not directly measured at the proximal airway using a Peumogard (Novametrix Medical Systems, Wallingford, Connecticut, United States) was calculated using a previously published formula.[13] Regression analysis between the measured (x) and the calculated (y) values showed a good linear correlation (r=0·92, regression coefficient=1·05, intercept=0·3 cm H_2O). So called ventilatory index (mean airway pressure × fractional inspiratory oxygen/oxygen tension) and the arterial:alveolar oxygen ratio (a/A PO_2) were calculated as previously described.[14] The requirements for fractional inspiratory oxygen a/A PO_2 ratio, mean airway pressure, ventilatory index, peak inspiratory pressure, positive end expiratory pressure, ventilator rate, and blood gases were recorded at 1 (SD 0·5), 12 (SD 2), and 24 (SD 2) hours and thereafter at intervals of 24 hours until the age of 10 days.

The clinical diagnosis of bronchopulmonary dysplasia was made on the basis of two criteria.

(1) Respiratory distress and supplemental oxygen required for longer than 28 days.

(2) Persistent strands of densities in both lungs, alternating with areas of normal or increased lucency, or Northway radiographic stage 3–4.[15]

Cranial ultrasound scans were obtained serially, and intracranial haemorrhages were classified using the grading scale of Papile *et al.*[16] Necrotising enterocolitis was diagnosed on the basis of clinical manifestations: abdominal *x* ray showing pneumatosis intestinalis and air in the portal circulation. The diagnosis of retrolental fibroplasia was based on ophthalmological examination at postconceptional ages of 9 and 13 months.

Statistical evaluation. Biomedical Computer Program (BMPD statistical software, University of California Press, Berkeley, California, United States) was used for statistical calculations.

As this was the first study to evaluate the effect of inositol in the newborn and the animal studies were not relevant in terms of estimating the magnitude of any effect we elected at the beginning of the trial to examine the data when between 25 and 28 new patients were enrolled, to test whether continuing the study was justified. The present report represents the third interim analysis.

According to experimental data inositol accelerates synthesis of surfactant in the immature lung. It was therefore prudent to adopt outcome criteria that were similar to those used in surfactant substitution trials. Accordingly, the major outcome was categorised in two groups: (1) 'Intact' survival—that is, survival without bronchopulmonary dysplasia; (2) death or bronchopulmonary dysplasia, or both. According to analysis of our results during the years 1980–82 the occurrence of 'intact' survival was 50% in ventilated infants with RDS and birth weight less than 2000 g. We chose to limit the total number of infants to a maximum of 150—that is, enough to detect a 36% decline in the undesired outcome, assuming a type 1 error of 5% and a type 2 error of 10%.[17]

Outcome is affected by a number of prenatal and neonatal variables, and the treatment and control groups could have been accidentally unequal in terms of major prognostic variables. We therefore examined 63 prenatal and neonatal variables obtained from the medical charts. Multiple regression analysis was used to test whether some of the variables that tended to be different between the two groups actually affected the major outcome (BMDP 1R).

The initial severity of illness might have influenced the response to therapeutic intervention. We therefore adjusted for differences in severity in the groups treated with inositol or placebo using analysis of covariance (BMPD IV). Fractional inspiratory oxygen and mean airway pressure before treatment with the sugars was begun at 12 hours were chosen as the respective covariates. This model assumed that the chosen pretreatment variable was related to the treatment response and that the variables concerned were normally distributed. The method of covariance analysis should reduce the estimate of experimental error and thus offer a more precise comparison between the two treatments. The skewness of the variables in each age group sampled was not different from those in a normal distribution. If inositol was indeed effective in decreasing the severity of RDS by means of increasing synthesis of surfactant the effect would probably be evident more than 48 hours after beginning treatment.[18] Pretreatment values at the age of 12 hours were related, therefore, to fractional inspiratory oxygen and mean airway pressures on days 4–8. In addition, possible differences between the groups treated with inositol and placebo were evaluated using analysis of variance (BMDP 4V) unpaired Student's t test, with or without equality of variances. Equality of

Table 1 *Prenatal characteristics of the two treatment groups*

	Treatment group	
	Inositol	*Placebo*
Single parent	2	8
Bleeding	8	13
Pre-eclampsia	13	13
Essential hypertension	2	0
Asphyxia	28	22
Tocolytic beta agonist	23	20
Mother on steroids	1	4
Caesarean section	27	23
Maternal smoking	6	9

Table 2 *Infant characteristics in the two treatment groups*

	Treatment group	
	Inositol	*Placebo*
Birth weight:		
Mean (SD)	1276 (321)	1256 (387)
Range	600–1860	600–1940
No > 1500 g	9	10
No <1000 g	8	11
Gestational age (weeks):		
Mean (SD)	29·5 (2·0)	29·5 (2·1)
Range	25·4–33·0	25·0–33·4
No > 31·0 weeks	9	10
No <28·0 weeks	12	12
Small for gestational age (<10th centile)	2	6
Singletons	31	32
Twins	6	4
Triplets	0	1
Sex (M/F)	20/17	18/19
Apgar score at one minute:		
≤3	12	14
4–6	15	12
≥7	10	11
Apgar score at five minutes:		
≤3	2	3
4–6	11	9
≥7	24	23
Intubated and ventilated at birth	30	25
Mean (SD) first systolic blood pressure (mmHg)	49 (9)	54 (10)
First tracheal aspirate:		
Mean (SD) lecithin: sphingomyelin ratio	1·1 (0·4)	1·0 (0·3)
Phosphatidylglycerol	0	0

variances was tested using Levene's test. Finally, the proportion of infants in each group with various morbidities or deaths was compared using the χ^2 test or Fisher's exact test.

Results

Of the 83 infants who entered the trial, nine did not fulfil the entrance criteria and were excluded from final analysis. Three had a high lecithin:sphingomyelin ratio and detectable phosphatidylglycerol in tracheal aspirate at birth. Two of these three infants (one in the inositol and one in the placebo group) improved immediately when the mechanical ventilation was decreased and the other (in the placebo group) improved after closure of the ductus arteriosus. Two infants (in the inositol group) had RDS on the basis of the tracheal phospholipid analysis but did not qualify because the duration of their respiratory distress was too short. Two infants (one from each group) died of respiratory failure before the beginning of supplementation. One infant (in the inositol group) had congenital heart disease and another (in the control group) had group B streptococcal sepsis and subsequently died.

Thus 74 infants fulfilled the study criteria, and 37 were assigned to the inositol group and 37 to the placebo group. To ascertain that the two randomised groups did not differ from each other, 35 prenatal variables describing maternal characteristics and obstetric management were compared. No significant differences were apparent (Table 1).

A further 28 neonatal variables describing the condition and treatment in the infants before the beginning of treatment with inositol or placebo were evaluated, and again there were no significant differences (Table 2).

The two groups did not differ from each other in respect of fractional inspiratory oxygen, blood gases, or ventilatory measurements during the first 48 hours. Between days 4 and 10, however, the infants treated with inositol tended to have a milder respiratory course than the control infants. The infants treated with inositol tended to require less fractional inspiratory oxygen, although the difference was not significant. The a/A PO_2 ratio tended to be higher in infants treated with inositol than in control infants (Fig. 1). Between days 4 and 8 the mean airway pressure was lower in infants in the inositol group than in the control group (BMDP IV, $p<0\cdot05$; BMDP 4V, $p<0\cdot01$). The ventilatory index tended to be significantly lower among the infants treated with inositol between days 4 and 7 (Fig. 2). In addition, during days 8 to 10, fewer infants in the inositol group required mechanical ventilation than in the control group ($p<0\cdot05$).

To analyse these differences further, the arterial blood gases and respirator settings were compared. Only the ventilator rates tended to be different (Fig. 3). Infants in the inositol group required slower rates than the control infants during days 5 to 7 ($p<0\cdot02$).

Fewer infants treated with inositol died or developed bronchopulmonary dysplasia compared with control infants (Table 3). The inositol group also had a tendency towards a lower incidence of pneumothorax and failure of indomethacin induced closure of patent ductus arteriosus. There was no detectable difference, however, in the incidence of intraventricular haemorrhage. Most of the babies

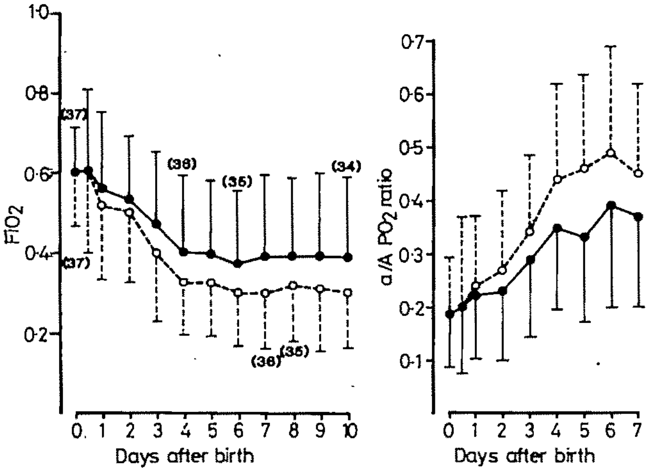

Fig. 1 *Fractional inspiratory oxygen (FiO_2) requirements and arterial-alveolar oxygen tension ratios (a/A PO_2) in the two study groups. ○=Mean (SD) values for the inositol group; ●=mean (SD) values for the control group. Numbers in parentheses indicate number of infants and decrease because of death. The a/A PO_2 is not shown beyond the first week because measurements of oxygen tension were not always available.*

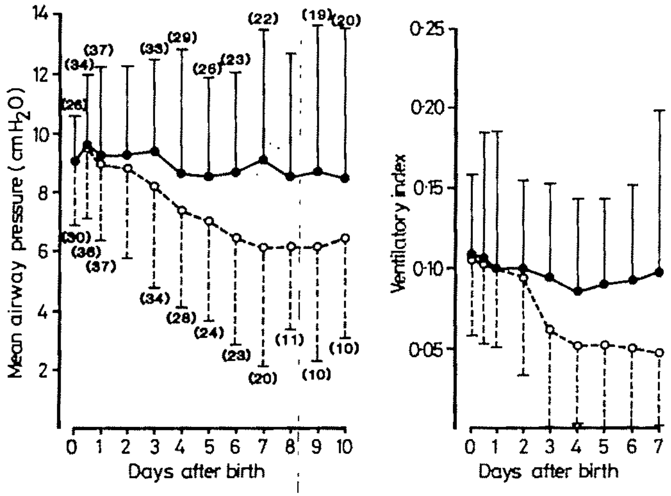

Fig. 2 *Mean airway pressure and ventilatory index (mean airway pressure × (fractional inspiratory oxygen/oxygen tension)) among the ventilated infants. ○=Mean (SD) values for the inositol group; ●=mean (SD) values for the control group. Numbers in parentheses indicate number of ventilated infants in each group. During days 8–10 significantly fewer infants in the inositol group than in the placebo group required mechanical ventilation (p<0·05). Ventilatory index is not shown beyond the first week because measurements of oxygen tension were not always available.*

Conversion: traditional to SI units—Ventilatory index: 1 mm Hg=0·076 kPa.

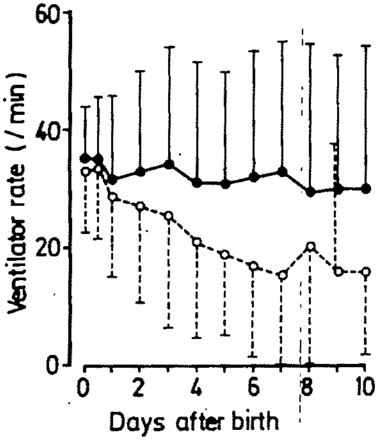

Fig. 3 *Mean (SD) ventilator rate among infants in the inositol (○) and control (●) groups.*

died from RDS or bronchopulmonary dysplasia (Table 4). Of the surviving infants with bronchopulmonary dysplasia, six required supplemental oxygen between 1 and 2 months (two in the inositol and four in the placebo group), five between 2 and 6 months (one in the inositol and four in the placebo group), and two more than 6 months (one in each group). Nine of the surviving infants with bronchopulmonary required mechanical ventilation after the neonatal period. All surviving infants are being followed up.

To assess whether the differences in the outcome were due to treatment with inositol rather than to confounding factors, multiple linear regression analyses were performed to assess the influence of some prenatal factors (gestational age, small for gestational age, single parent, bleeding, and mother on steroids) on the outcome. Only gestational age correlated significantly (p=0·05) with poor outcome (death or bronchopulmonary dysplasia, or both=0; good outcome=1). Figure 4 shows outcome according to gestational age.

Table 3 *Morbidity and mortality in the two treatment groups*

	Treatment group		*p Value*
	Inositol	*Placebo*	
Deaths*	5	10	
Bronchopulmonary dysplasia	5	11	
Death or bronchopulmonary dysplasia, or both	9	19	<0·02
Pneumothorax	5	11	<0·1
Pulmonary interstitial emphysema	5	10	
Patent ductus arteriosus	27	27	
Treatment of patent ductus arteriosus:			
None	6	4	
Indomethacin	21	23	
Indomethacin+ligation	5	10	
Indomethacin failure	5	12	<0·05
Necrotising enterocolitis	1	2	
Retrolental fibroplasia	1	4	
Infections:			
0–7 days	2	2	
8–28 days	5	9	
Intraventricular haemorrhage:			
None	23	23	
I or II	12	9	
III or IV	2	5	

*All infant deaths that were related to neonatal condition were included. There was additionally one case of sudden infant death syndrome in the placebo group.

Table 4 *Causes of death and related data in the two treatment groups*

Case No	*Birth weight (g)*	*Gestational age (weeks)*	*Age at death (days)*	*Autopsy findings related to death**
Inositol group				
1	600	26·9	7	Massive intracerebral haemorrhage, hyaline membrane disease (stopping of ventilatory support)
2	890	27·0	210	Bronchopulmonary dysplasia, cor pulmonale
3	1245	29·6	16	Necrotising enterocolitis, hyaline membrane disease, cerebral necrosis and infarcts (birth asphyxia)
4	1860	30·6	8	Total cerebral necrosis, respiratory distress syndrome, pneumonia (birth asphyxia)
5	1380	31·7	16	Severe respiratory distress syndrome, necrosis corticalis renis (birth asphyxia)
Placebo group				
1	1200	27·0	14	Severe respiratory distress syndrome, interstitial emphysema
2	850	27·0	225	Bronchopulmonary dysplasia, tracheal perforation, pneumothorax
3	920	25·8	5	Sepsis, hyaline membrane disease, intracerebral haemorrhage
4	615	28·6	15	Hyaline membrane disease, cerebral infarct, renal cortical necrosis
5	1760	31·1	4	Respiratory distress syndrome, intraventricular haemorrhage, renal cortical necrosis (birth asphyxia)
6	970	26·7	23	Candidiasis, hyaline membrane disease, intraventricular haemorrhage
7	1080	29·7	28	Obstructive tracheobronchitis, superior vena cava thrombosis
8	1320	30·7	13	Respiratory distress syndrome, renal failure, intracerebral haemorrhage
9	600	27·4	36	Bronchopulmonary dysplasia
10	1410	31·0	10	Massive intracerebral haemorrhage, respiratory distress syndrome (stopping of ventilatory support)

*Following cases had histological grade 3 bronchopulmonary dysplasia on autopsy: inositol: 3 and 5, placebo: 1, 4, and 7.

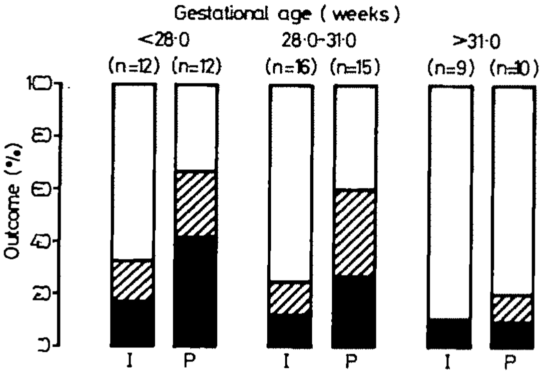

Fig. 4 *Outcome of infants according to gestational age. I=group treated with inositol; P=group treated with placebo. Black areas represent deaths; hatched areas represent infants with bronchopulmonary dysplasia.*

Discussion

This randomised double blind trial involving preterm infants with RDS provides the first evidence that supplementation with inositol decreases the ventilatory needs and moderates the course of respiratory failure. In addition, there were fewer deaths or cases of bronchopulmonary dysplasia among the infants treated with inositol. The result may seem surprising because inositol had no immediate effects on ventilatory requirements or blood gases. In contrast, effective treatments of respiratory failure have had a direct, immediate effect on lung function thus reversing the progressive course of respiratory failure, decreasing the incidence of severe complications, and reducing the number of infants who eventually developed bronchopulmonary dysplasia. Despite this, no infant with RDS died within 48 hours after beginning treatment with the sugar, and only two died before the sugar was given. The respiratory support was effective enough in most cases, therefore, to allow sufficient time (about 48 hours)[9] for the effect of inositol to take place, and the study covered more than 90% of the population with RDS. The birthweight limit of less than 2000 g was chosen because the prognosis of RDS in this weight group is still poor, and oral feedings are often withheld.

Although inositol prevents the synthesis of the second major surfactant component, phosphatidylglycerol, the paucity of this phospholipid in RDS is not a cause but a consequence of lung immaturity.[19 20] According to current theory, inositol (inositol-phosphoinositide pair) augments the effect of glucocorticoid and thyroid hormone in the synthesis of surfactant phosphatidylcholine.[9] Phosphatidylglycerol may have a similar function.[9 21] The synthesis of phosphatidylglycerol in the immature lung is inactive, however, regardless of extracellular inositol concentration (Hallman M. Unpublished observations.), whereas inositol is easily available for synthesis of surfactant phosphatidylinositol in immature alveolar cells, provided that the serum inositol concentration is high.[21 22 2 3 10] Mandatory withholding of the breast milk feedings from sick preterm infants decreased serum inositol concentrations sometimes below those present in the immature fetus,[10] and low serum inositol concentrations in small preterm infants suffering from RDS were not associated with a favourable prognosis either.[3] The aim of the present study, therefore, was to 'normalise' the intake of inositol and to find out whether inositol affects the natural history of RDS.

Studies with somewhat similar objectives but with different drugs have been conducted before. Administration of cortisol to newborn infants with RDS did not affect the course of the disease.[23] One possible explanation for the lack of effect of glucocorticoids is the increase in serum cortisol concentration in RDS.[23] Also adverse effects of glucocorticoids possibly mask the beneficial ones or the time required for the beneficial effect of glucocorticoids was possibly too long.[18] Exogenous natural surfactant given in RDS has been shown to reduce oxygen and respirator pressure requirements and decrease the incidence of air leaks, death, and bronchopulmonary dysplasia.[14] There is conflicting information, however, about the efficacy of dry artificial surfactant in RDS.[24 25]

Although lack of surfactant is the principal cause of RDS and supplementation of surfactant possibly results in immediate amelioration of respiratory failure, a 'drug' that supposedly stimulates synthesis of surfactant cannot have a similar effect, as it requires time before a change in endogenous synthesis, secretion, and accumulation of surfactant into the airways takes place. None the less, both exogenous natural surfactant[14] and inositol reduced the severity of RDS, although the former had a more striking effect. Infants treated with inositol had fewer failures of indomethacin to close the patent ductus arteriosis compared with controls. It is difficult to conceive that all these effects were due to an increase in production of surfactant. Although there are no other explanations at present, it is possible that systems other than the surfactant depend on dietary inositol too.

Inositol-phosphoinositide pair serves as a 'tertiary' messenger of various functions associated with the cell membrane—for instance, secretion of many hormones (glucocorticoids, thyrotrophin releasing hormone, insulin, angiotensin, acetylcholine, and others), local factors (epidermal growth factor), transmission of nerve impulse, or function of white cells.[4 26] The evidence that inositol is important in reproduction and early development has been challenged,[8] and in view of the ubiquitous synthesis and active intracellular transport of this sugar it has been considered that the availability of inositol is not rate limiting in the transmitter functions concerned. This concept may not always be true because—for example, in experimental diabetic neuropathy—inositol supplementation restores neuronal inositol concentration and improves the abnormal peripheral nerve conduction velocity.[27]

Inositol is highly compartmentalised. Although a high affinity, sodium requiring active inositol transport is present in any tissue, the availability of inositol in a specific intracellular site may depend on a variety of factors, such as active inositol uptake, endogenous synthesis, permeability, and concentration gradient across the membrane. These determinants additionally change during perinatal development[21] or during disease.[27] It is therefore conceivable that phosphoinositide mediated functions critically depend on the availability of inositol.

The present data, showing evidence of the beneficial effect of inositol in RDS, is still preliminary. Several important questions remain. Only small preterm infants with RDS were treated. The beneficial effect was evident among those with gestational ages less than 31 weeks and weighing less than 1500 g. Newborns with renal failure were not treated as in uraemia the lack of renal inositol secretion and catabolism results in hyperinositolaemia.[28] The dose, duration of treatment, and other pharmacodynamic aspects of inositol remain unclear, and the possibility that it causes side effects has not been excluded either. Long term follow up of the infants is in progress. Nevertheless, the present results support the concept that some substrates have specific roles in differentiation and raise a question whether immature newborn infants or some high risk fetuses need an adequate supply of a wider range of nutrients than considered necessary at present.

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Thiopentone induced coma after severe birth asphyxia

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SUMMARY The aim of this study was to determine the feasibility of inducing a prolonged coma in severely asphyxiated newborn babies by the infusion of high dose thiopentone. In six severely asphyxiated babies the electroencephalograph (EEG) and blood pressure were monitored continuously. Thiopentone was infused at a rate sufficient to suppress completely the EEG providing the mean blood pressure remained above 35 mm Hg; it was continued until there was no evidence of cerebral oedema for 24 hours. In two the infusion was stopped prematurely because of hypotension that was unresponsive to treatment. In the other four a deep coma was maintained for a median duration of 127 hours. All developed pharmacodynamic tolerance to the thiopentone and showed non-linear elimination kinetics. Three babies died; the three survivors have moderate to severe handicap. It was concluded that with full intensive care it is possible to induce a deep coma; the outcome does not seem to be improved, however, and the incidence of complications was high.

Babies born without a heart beat who despite resuscitation do not start to breathe spontaneously within the first half hour after birth have a poor outcome.[1–3] In a large study, babies with an Apgar score of three or less for more than 20 minutes had a mortality of 87% and the rate of cerebral palsy in survivors was 57%.[4] Monitoring of heart rate and sonography are used to identify the fetus at risk of intrapartum asphyxia, but despite this some are born profoundly asphyxiated. Although death results from damage to organs other than the brain, long term morbidity is almost exclusively a consequence of impaired brain function.

There is debate about the management of postasphyxial encephalopathy. Severe restriction of fluid intake to reduce production of cerebrospinal fluid and prevent cerebral oedema has not been shown to be beneficial and may result in depletion of intravascular volume and hypotension.[5] Hyperventilation decreases raised intracranial pressure only by reducing cerebral blood flow; if there is associated hypotension from myocardial ischaemia or hypovolaemia hyperventilation may lead to further neuronal injury. Although steroids are often given, there is no evidence of a reduction in the cerebral oedema after hypoxia, ischaemia, or trauma.[6] Hyperosmotic diuretics can decrease intracerebral interstitial fluid and lower intracranial pressure. When there is increased vascular permeability from hypoxia, however, influx of hyperosmotic fluid may increase the intracranial water content further and lead instead to a rise in intracranial pressure.[5]

Barbiturates have been shown to induce a reversible depression of neuronal function, cerebral metabolic rate, and blood flow.[7] These effects are dependent on dose until the electroencephalogram (EEG) is isoelectric when cerebral metabolic rate and blood flow are reduced by 50%.[8] The reduced cerebral blood flow is associated with an increased cerebrovascular resistance and reduced cerebral blood volume. This may explain the accompanying reduction in intracranial pressure.[8] In addition, it has been suggested that barbiturates stabilise lysosomal membranes, quench oxygen free radicals, reduce intracellular calcium concentrations, and modify amino acid and neurotransmitter release from the neurone.[9]

When given to animals before generalised cerebral ischaemia high doses of barbiturates protect the newborn and fetal brain.[10–13] This effect, however, has not been found consistently after global cerebral ischaemia in mature animals.[9] Barbiturates given before or sometime after cerebrovascular occlusions reduce the area of infarction in many species.[14–16] In primates subjected to permanent middle cerebral artery occlusion the reduction in the size of the infarction is proportional to the dose until there is maximal suppression of neuronal activity.[17 18] A beneficial effect has been shown even when treatment with barbiturates was delayed up to two hours after the occlusion.[14 15 18 19] When vascular occlusion has been followed by re-perfusion coma induced by the barbiturate, started after 30 minutes and maintained for 96 hours, provides nearly complete protection.[20]

In view of these findings we designed a study to investigate the possibility of using treatment with high dose barbiturate for newly born babies who had sustained very severe intrapartum asphyxia.

Patients and methods

Babies born between May 1980 and December 1982 in the John Radcliffe Maternity Hospital, Oxford, were eligible for the study if there was no heart beat at birth and despite resuscitation they failed to establish spontaneous respiration within 20 minutes after birth. Babies with obvious lethal congenital malformations were excluded.

Thiopentone was selected as the most appropriate barbiturate because it is highly lipid soluble; thus high concentrations can be achieved in neurones within seconds of an intravenous bolus.

After resuscitation had been performed and a regular heart beat established the babies were transferred to the intensive care nursery. The possible benefits and side effects of an infusion of thiopentone were discussed with one or both parents as soon as possible and before starting the infusion. Their consent for this treatment was obtained. Umbilical arterial and venous catheters were inserted and the aortic blood pressure and the central venous blood pressure were monitored continuously. A two channel EEG was recorded continuously, using a method described previously.[21] If the mean aortic blood pressure was greater than 35 mm Hg an infusion of a 2·5% solution of thiopentone in water was started through the central venous catheter. A loading dose of 10 mg/kg of thiopentone was given over 30 minutes. In the next hour a further dose of 10 mg/kg was given. Thereafter, the rate of infusion of thiopentone was reduced to 2 mg/kg/h and subsequently adjusted to keep the EEG isoelectric.

If the mean aortic blood pressure fell below 35 mm Hg and the central venous blood pressure was less than 12 cm H_2O plasma was infused. If the mean aortic blood pressure fell below 30 mm Hg the infusion of thiopentone was stopped, but if it did not rise above 35 mm Hg in the subsequent half hour an infusion of dopamine was started at 2 μg/kg/min, increasing to a maximum of 10 μg/kg/min. When the mean aortic blood pressure was above 35 mm Hg the infusion of thiopentone was restarted.

All babies received intermittent positive pressure ventilation, and arterial blood gases were measured at least four hourly. The oxygen tension was maintained between 6·6 and 11·3 kPa (50–85 mm Hg) and the carbon dioxide tension between 3·7 and 4·6 kPa (28–35 mm Hg). The intake of non-colloid fluid was 60 ml/kg/24h, given intravenously.

An ultrasound scan of the brain was performed daily. Myocardial function was assessed by electrocardiograph (ECG) daily and by echocardiography. Blood glucose concentration was measured three hourly, plasma thiopentone concentration six hourly, and plasma electrolyte concentrations and liver function tests daily.

The infusion of thiopentone was continued until there was a 24 hour period with no evidence of raised intracranial pressure based on clinical examination and cerebral ultrasonography. Babies who died had a postmortem examination, which

Table 1 *Clinical characteristics of the patients*

Case No	*Sex*	*Gestation (weeks)*	*Weight (g)*	*Duration of labour*		*Method of delivery*	*Time from birth to onset of*		*First blood pH*
				First stage (h)	*Second stage (min)*		*Heart beat (min)*	*Respiration (min)*	
1	M	40	4270	4·5	23	SVD	2	25	7·05*
2	M	41	3430	10·5	30	KFRD	10	20	7·00*
3	M	41	3400	30·3	60	KFRD	5	120	6·59*
4	F	40	3230	3·8	51	NBFD	10	90	6·89†
5	F	40	3480	11·5	77	Ventouse	20	Never	6·87*
6	F	41	3740	Cord prolapse		Ventouse failed; LSCS	3	150	6·75†

SVD=Spontaneous vaginal delivery.
KFRD=Kejlland's forceps rotational delivery.
NBFD=Neville Barnes forceps delivery.
LSCS=lower segment caesarean delivery.
*Arterial blood taken after resuscitation and treatment with bicarbonate.
†Umbilical arterial blood.

included a histological examination of the brain. A clinical examination, intellectual assessment by the Griffiths scale, and assessment of visual and auditory function was carried out on the surviving babies at the age of 3 years.

Results

Altogether, 15 522 babies were born during the 32 months of the study. Six babies fulfilled the criteria for entry, which represented an incidence of 0·4/1000 live births each year.

The clinical characteristics of the babies studied are summarised in Table 1. Two patients (cases 3 and 4) were monitored by cardiotocography during labour and had evidence of fetal distress. Case 3 had a fetal tachycardia of ≥180 beats/min, with loss of variability for three hours before delivery. Case 4 had late decelerations in heart rate for two hours followed by a fetal bradycardia of less than 60 beats/min for 35 minutes before delivery. There was meconium staining of the liquor during the labour of cases 2 and 5. Cases 1, 2, and 4 had the umbilical cord tightly around their necks at the time of delivery.

The median time between birth and starting the infusion of thiopentone was 115 minutes, with a range of 60–140 minutes. The maximum plasma thiopentone concentrations measured during each 24 hour period during and after the stopping of the infusion are shown in Figure 1. In cases 2 and 5 the infusion was stopped after five and 30 hours, respectively, because of hypotension that was unresponsive to an infusion of dopamine. The remaining four babies completed the study. The median duration of the infusion of thiopentone in these babies was 127 hours, with a range of 86–169 hours. In all four progressively increasing plasma concentrations of thiopentone were required to maintain an isoelectric EEG. Neurological examination during the barbiturate coma was uninformative; even deep tendon, occipitocephalic, and corneal reflexes were abolished. The pupils remained constricted and were non-reactive to light.

After stopping the infusion the rate of thiopentone elimination was measured in cases 3, 4, and 6

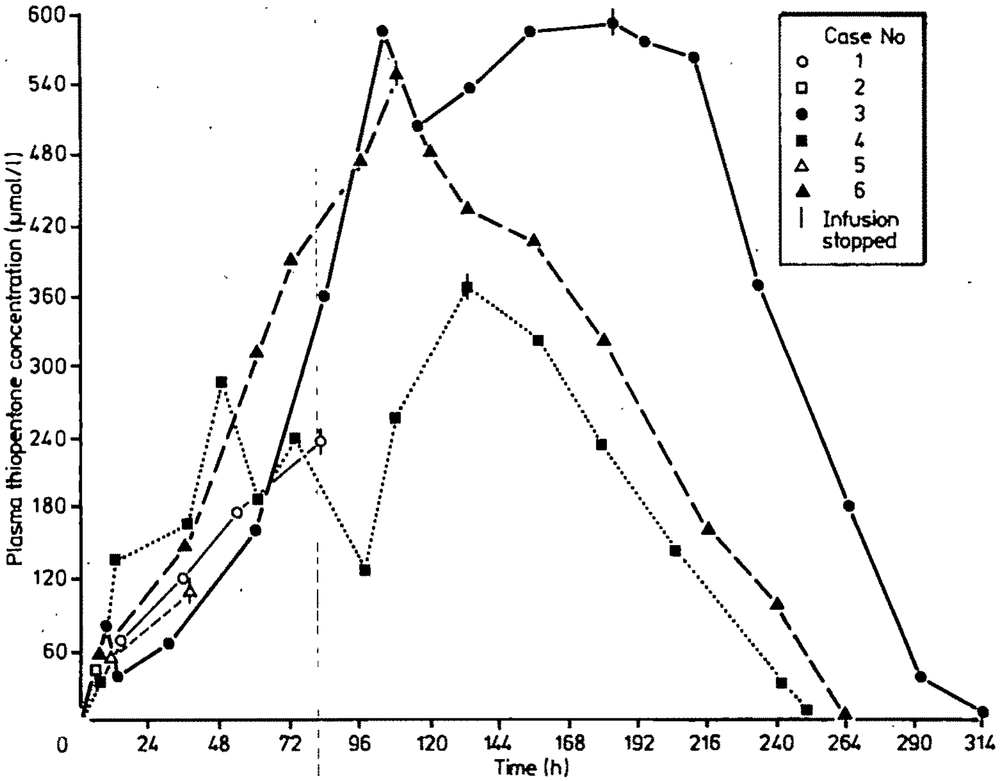

Fig. 1 *Plasma thiopentone concentrations in the six infants from the onset of infusion.*

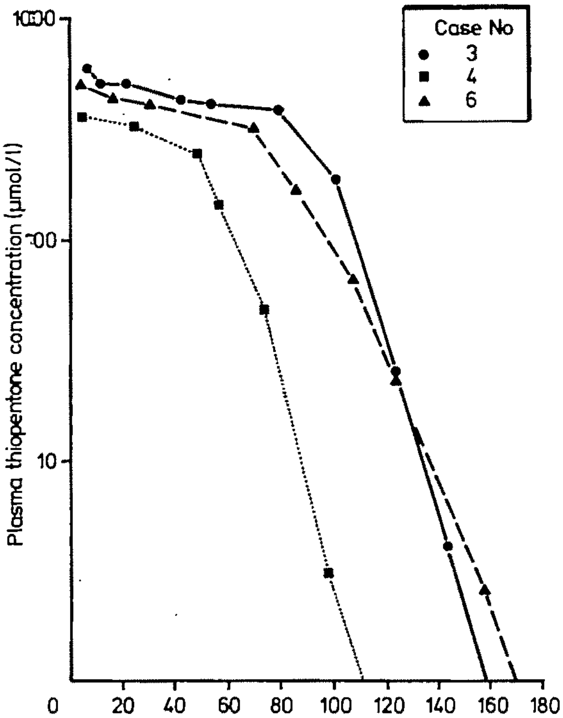

Fig. 2 *Clearance of thiopentone in case 3, 4, and 6 after stopping the continuous infusion.*

(Fig. 2). The rate of thiopentone clearance was not constant, rather it slowly increased with time, indicating the presence of non-linear elimination kinetics. Cases 3 and 6 began to show clinical evidence of cerebral activity (movement in response to a noxious stimulus) at plasma thiopentone concentrations of less than 187 and 165 µmol/l 101 and 107 hours, respectively, after the infusion had been stopped. Case 4 sustained brain death and showed no clinical evidence of cerebral activity when the serum thiopentone concentrations were unrecordable.

The major side effects were dose-dependent cardiovascular and respiratory depression. The loading dose of thiopentone suppressed all spontaneous respiratory effort; all babies received intermittent positive pressure ventilation, the median period being 9·5 days, with a range of 3–20 days. In addition, four babies had early respiratory problems attributed to asphyxial lung injury. Soon after birth all six babies had ECG and ultrasound evidence of myocardial ischaemia or infarction. In all the heart rate and blood pressure fell after the beginning of the infusion of thiopentone (Fig. 3). In two (cases 2 and 5) an infusion of dopamine was used to support myocardial function All six babies had clinical evidence of acute tubular necrosis and all had initial low plasma calcium concentrations (less than 1·5 mmol/l (6mg/100ml)); two (cases 3 and 6) had one

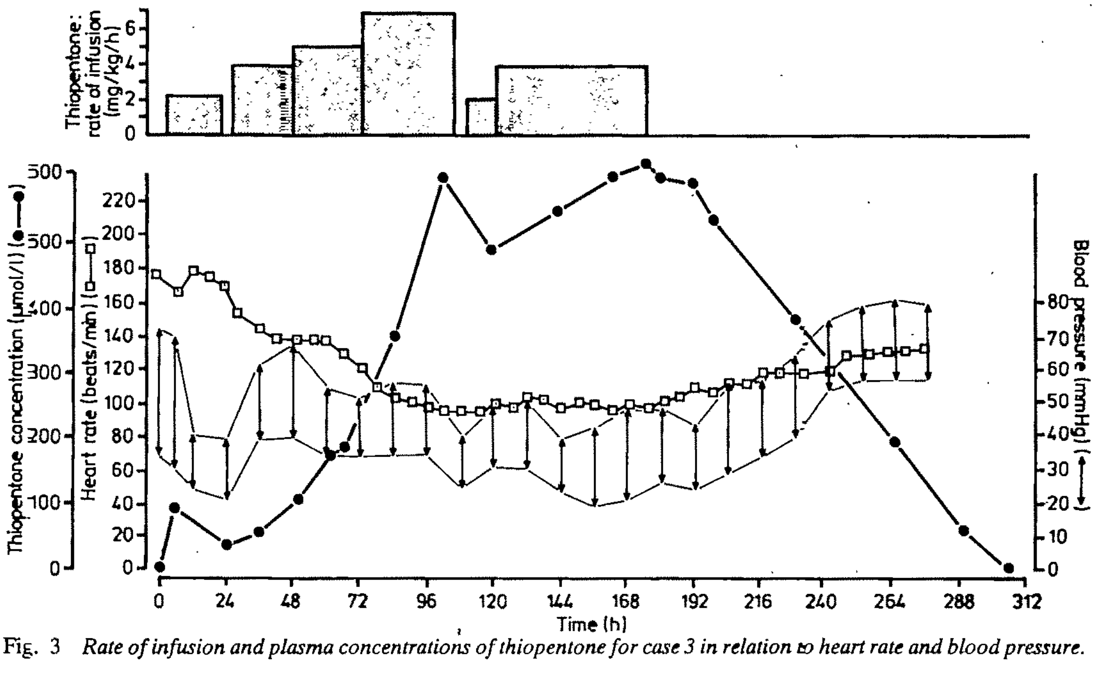

Fig. 3 *Rate of infusion and plasma concentrations of thiopentone for case 3 in relation to heart rate and blood pressure.*

Table 2 *Outcome of the patients*

Babies who survived.

Case No	*Age at last examination (years)*	*Clinical findings*			
		Motor	*Sensory*	*Intellectual*	*Other*
1	5	Mild spastic diplegia	—	Moderate retardation	—
2	4	Severe dystonic cerebral palsy	—	Normal	—
6	3	Severe spastic quadriplegia	—	Severe retardation	Epilepsy; microcephaly

Babies who died.

Case No	*Age at death*	*Post mortemfindings*			
		Brain	*Heart*	*Kidney*	*Liver*
3	8 months	Severe atrophy. Neuronal cell loss. Gliosis involving cerebral cortices, basal ganglia, thalamus, hypothalamus, and brain stem	Normal	Normal	Normal
4	13 days	Severe necrosis of the neurons of cerebral cortex, basal ganglia, thalamus, hypothalamus, corpus callosum, cerebellum, and brain stem	Normal	Vascular congestion	Normal
5	5 days	Anoxic haemorrhages. Early neuronal necrosis, involving cerebral hemispheres, basal ganglia, thalamus, hypothalamus, and brain stem	Biventricular infarction	Acute tubular necrosis	Centrilobular necrosis

hypoglycaemic episode (less than 1·1 mmol/l (19·8 mg/100 ml)). Three babies died (cases 3, 4, and 5), and three survived with serious disabilities (cases 1, 2, and 6). The outcome of the babies is tabulated in Table 2.

Discussion

The poor outcome of the survivors of this study was disappointing. The explanation may lie in the delay from the onset of cerebral ischaemia to the administration of the thiopentone. In the babies the neuronal ischaemia must have begun during labour and it is therefore difficult to determine the exact time of onset for each baby. Only two babies had cardiac tocographic monitoring during labour: both had evidence of fetal distress for more than two and a half hours before delivery. In addition, there was a delay from birth to the administration of thiopentone. During this time resuscitation was performed, the baby transferred to the intensive care nursery, catheters placed in the aorta and inferior vena cava, monitoring of pressure begun, and parental consent obtained. The total time from the onset of neuronal ischaemia to administration of thiopentone may have been up to four hours. Animal studies have shown a beneficial effect from thiopentone only when it was administered up to two hours after the onset of neuronal ischaemia.

The major side effect of the infusion of thiopentone was cardiovascular suppression. It has been shown that this myocardial toxicity will be potentiated if the myocardium is compromised or if intravascular volume is depleted. There was clinical evidence of myocardial ischaemia in all six babies studied, and cardiovascular suppression was evident in all six immediately after administering the first dose of thiopentone. If episodes of hypotension and thus further cerebral ischaemia are to be avoided in very severely asphyxiated babies it is important to monitor both arterial and central venous blood pressures before starting the infusion of thiopentone. In addition, it is necessary to assess cardiac function regularly by clinical examination, ECG, and echocardiography.

To keep the EEG suppressed the serum thiopentone concentrations had to be progressively increased. A similarly rapid onset of pharmacodynamic tolerance has been described previously in adult patients,[22] but its mechanism is unknown. The rapid development of tolerance makes continuous recording of the EEG mandatory as it provides the only guide to the necessary rate of infusion of the thiopentone. Thiopentone is almost completely metabolised by a hepatic microsomal system, with only 0·3% being recovered unaltered in human urine.[23] When used in low doses (5 mg/kg)—for example, as a bolus for the induction of anaesthesia—thiopentone shows first order kinetics with a half life in neonates double that of adults (16 hours and eight hours, respectively).[23] In this study after prolonged administration thiopentone showed non-linear kinetics, and initially there was a very slow clearance of thiopentone from the blood. This non-linearity is probably a consequence of the saturation of the hepatic enzyme system that oxidises thiopentone to an inactive carboxylic acid metabolite. This has important therapeutic implications: when the infusion is stopped after a prolonged period the subjects remained comatosed for many days. Intensive care must continue during this time, and it is impossible to make a detailed assessment of neurological function. Such a long period of coma and uncertainty immediately after a difficult delivery is stressful both to the parents and to the medical and nursing staff caring for the baby.

This study shows that treatment with high dose thiopentone is possible in the newborn after severe intrapartum asphyxia but that it requires full intensive care and extremely close medical and nursing supervision. When begun one to two hours after birth the outcome does not seem to be improved and the incidence of complications is high.

We thank Professor Sir Peter Tizard for his advice, Dr J Keeling and Dr M Esiri for performing the postmortem examinations, and Mrs P McEwen for typing the manuscript.

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Head size, brain growth, and lateral ventricles in very low birthweight infants

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SUMMARY Ninety eight newborn infants weighing <1500 g at birth and with gestational ages from 26 to 32 weeks were followed prospectively. They were grouped according to real time ultrasound scans in the neonatal period: infants in group A (n=20) had periventricular haemorrhage (PVH) and normal ventricles; infants in group B (n=26) had PVH and dilated ventricles (none with clinical hydrocephalus); and infants in group C, who formed the control group (n=52), had no PVH and normal ventricles. At outpatient follow up a static image ultrasound scanner was used to measure the width of the lateral ventricles and brain hemispheres. The three groups of infants showed similar growth in occipitofrontal circumference, biparietal diameter, and brain hemispheres irrespective of a history of PVH or ventricular dilatation. The relation of ventricle size to biparietal diameter was similar in those infants in groups A (PVH alone) and C (controls) who had a good outcome. About a third (n=8) of the infants in group B had persistent ventricular dilatation in relation to biparietal diameter and a poor outcome associated with developmental delay and cerebral palsy. By contrast, the remaining two thirds (n=18) of the infants in group B who later had smaller ventricles in relation to biparietal diameter showed fewer neurodevelopmental sequelae. It is suggested that persistent ventricular dilatation in relation to biparietal diameter at follow up carries a bad prognosis, which might be due to brain atrophy.

Ultrasound scanning of the neonatal brain is a major advance in the diagnosis of periventricular haemorrhage (PVH). Most studies report such haemorrhages in about 50% of preterm infants weighing less than 1500 g, and the prevalence of haemorrhage is higher in infants under 1000 g at birth.[1-3] Palmer *et al* have shown that infants with PVH and ventricular dilatation do not progress as well in their later development as infants with PVH alone.[4] Usually, ventricular dilatation occurs in infants who have sustained moderate to severe PVH, but both Palmer *et al* and Stewart *et al* have occasionally noted ventricular dilatation occurring after small haemorrhages in the subependymal area and within the ventricles.[4 5] Progression to clinical hydrocephalus carries a poor prognosis, due to cerebral palsy, developmental delay, and deficits in hearing and vision in later childhood.[5] This has raised concern that our usual practice of not intervening in infants with ventricular dilatation until there is rapid head growth and signs of raised intracranial pressure may allow unnecessary neurological damage.

Little is known about the natural history of ventricular dilatation after PVH in infants who do not develop clinical hydrocephalus. We report here our findings on later head growth and growth of the lateral ventricles and of the brain hemispheres in an unselected series of very low birthweight infants.

Patients and methods

Infants. Ninety eight newborn infants born at St Mary's Hospital between 1980 and 1983 with birth weight <1500 g and gestational age 26–32 weeks who survived the neonatal period were followed up prospectively. Their clinical details are shown in Table 1. A real time ultrasound sector scanner fitted with a 5 mHz transducer was used for carrying out neonatal brain scans.[6 7] In 20 infants there was haemorrhage in the germinal layer, and in eight of

Table 1 *Clinical details of the 98 infants studied*

	Group A (PVH alone; n=20)	*Group B (PVH and ventricular dilatation; n=26)*	*Group C (normal controls; n=52)*
Delivery			
Vertex	10	11	20
Breech	1	2	3
Forceps	0	1	1
Caesarean section	9	11	28
Face	0	1	0
Mean (SD) gestational age (wks)	29·6 (1·9)**†	28·1 (2·4)***	30·8 (2·1)
Mean (SD) birth weight (g)	1139 (168)*	1093 (202)***	1256 (179)
Mean (SD) occipitofrontal circumference (cm)	25·7 (1·3)*	26·4 (1·1)***	27·1 (1·5)
Neonatal conditions:			
Idiopathic respiratory distress	12	14	26
Jaundice	19	26	49
Septicaemia	6	14	9
Patent ductus arteriosus	6	10	9
Apnoeic attacks	4	11	11
Pneumonia	8	14	5
Necrotising enterocolitis	2	7	9
Pneumothorax	4	3	2
Hypoglycaemia	2	3	1
Congenital anomaly (hydrocele, dislocated hip, hernia)	2	3	2

Group A *v* group C:* $p<0{\cdot}05$,** $p<0{\cdot}01$; Group B *v* group C:\*** $p<0{\cdot}001$; Group A *v* group B:† $p<0{\cdot}05$.

these infants the haemorrhage extended into the ventricles but without causing obvious dilatation, in that the width of the body of the lateral ventricles was between the 3rd and 97th centiles for gestational age.[6] These formed group A (PVH and normal sized ventricles). In 26 infants the haemorrhage had entered the ventricles and caused dilatation (> 97th centile[6]), and these formed group B (PVH and dilated ventricles). In three of these infants haemorrhage had extended into the brain parenchyma. The remaining 52 infants had no PVH and normal sized ventricles (3rd to 97th centile[6]) and formed group C (controls). The infants were discharged from hospital by their estimated date of delivery (40 weeks postconceptional age). Five infants with clinical hydrocephalus (increase in occipitofrontal circumference about 2 cm/week and crossing centile lines[8]) who had received neurosurgical treatment were excluded; otherwise all infants born when ultrasound was available were included.

Follow up. At each clinic visit the occipitofrontal circumference was measured with a paper measuring tape, biparietal diameter with steel callipers, and width of the lateral ventricles and brain hemispheres by static image (grey scale) ultrasound.[9]

Width of the lateral ventricles and brain hemispheres. A static image ultrasound scanner, with a 2·25 mHz transducer, was used. The infant was placed recumbent with his head in the true lateral position. The scanning arm was placed perpendicular to the infant's head, with gel between the transducer probe and the head. Scans were made at 5 mm intervals from the external auditory meatus to the vertex, parallel to the canthomeatal line. As echoes from the interface between transducer and skin interferred with the quality of images from the same side the dimensions of the lateral ventricle and brain hemisphere were measured on the contralateral side. The infant's head was turned to obtain measurements on the other side. The measurements were made with electronic callipers, at the level of the mid-body of the lateral ventricle, from the midline echo to the first strong echo of the lateral ventricular wall. The hemisphere was measured at the same level from the midline echo to the first strong echo of the inner table of the skull. The standard error of our measurements was 1% or less. Each infant had between three and five ultrasound scans during follow up in the first year.

Developmental assessment. The Griffiths' scale was used in assessments in the second year,[10] and a developmental quotient was used to indicate the overall level of development as suggested by Palmer *et al.*[4] When abnormal vision or hearing was suspected the infants were referred for specialised ophthalmological and audiometric assessments.

Data analysis. Differences in mean values were compared by Students' t test. Differences in the frequency of proportions between two groups of infants were compared by the χ^2 test or Fisher's exact test where appropriate. Growth curves were fitted to longitudinal data on the rates of increase in occipitofrontal circumference or biparietal diameter, using an exponential decay model, $y=ae^{-bx} + c$. Linear regression analysis ($y=ax + b$) was used in evaluating the relation of ventricle size to biparietal diameter.

Results

The clinical details in Table 1 show that infants in groups A and B were born earlier than infants in group C. Consequently, infants with PVH (groups A or B) had lower birth weights and smaller occipitofrontal circumference values than those in group C, but the differences were fairly small. Mode of delivery and neonatal complications were similar in the three groups of infants. When the infants were followed up their postnatal age was corrected for prematurity.

Occipitofrontal circumference, biparietal diameter, lateral ventricles, and brain hemispheres in the first year. The data within each subgroup (divided according to estimated date of delivery up to 16 weeks, 17–33 weeks, and 34–50 weeks) in Table 2 are normally distributed, and the timing of measurements were similar in all three groups. The mean occipitofrontal circumference and mean biparietal diameter in the three groups were statistically similar, although infants in group B had larger ventricles. The measurements of left hemisphere and right hemisphere in the three groups were also similar, so it seems that infants in group B with larger ventricles had a narrower width of brain tissue.

Growth rates in occipitofrontal circumference and biparietal diameter. All three groups had similar growth rates in occipitofrontal circumference and biparietal diameter. Thus the growth rates were not significantly affected by PVH or ventricular dilatation. The growth trajectory in each group showed a progressive decline in velocity (cm/wk) from the estimated date of delivery onwards during the first year (Fig. 1). The period of maximal head growth seemed to extend for a period of about 16 weeks after the estimated date of delivery.

Table 2 *Mean (SD) [No of observations] occipitofrontal circumference, biparietal diameter, lateral ventricles, and brain hemispheres (cm) in the first year*

Corrected postnatal age (wks)	*Group A (PVH alone; n=20)*	*Group B (PVH and ventricular dilatation; n=26)*	*Group C (normal controls; n=52)*
Occipitofrontal circumference			
EDD–16	38·26 (2·56) [30]	37·76 (2·73) [43]	37·68 (2·51) [83]
17–33	42·55 (1·14) [22]	42·19 (2·36) [27]	42·56 (1·59) [61]
34–50	44·79 (1·14) [19]	44·31 (1·83) [25]	44·70 (1·42) [46]
Biparietal diameter			
EDD–16	9·45 (0·76)	9·37 (0·77)	9·40 (0·80)
17–33	11·15 (0·45)	10·99 (0·71)	11·19 (0·47)
34–50	11·74 (0·48)	11·44 (0·75)	11·83 (0·46)
Left ventricle			
EDD–16	1·44 (0·13)	1·53 (0·18)*	1·41 (0·14)
17–33	1·70 (0·18)	1·69 (0·14)	1·64 (0·15)
34–50	1·70 (0·11)	1·82 (0·19)	1·71 (0·13)
Right ventricle			
EDD–16	1·46 (0·13)	1·54 (0·25)*	1·40 (0·15)
17–33	1·63 (0·19)	1·69 (0·14)	1·63 (0·14)
34–50	1·72 (0·12)	1·80 (0·23)	1·72 (0·10)
Left hemisphere			
EDD–16	4·28 (0·34)	4·32 (0·40)	4·30 (0·39)
17–33	5·16 (0·36)	5·07 (0·37)	5·14 (0·30)
34–50	5·46 (0·26)	5·30 (0·40)	5·54 (0·27)
Right hemisphere			
EDD–16	4·25 (0·33)	4·28 (0·37)	4·28 (0·38)
17–33	5·11 (0·30)	5·10 (0·33)	5·11 (0·30)
34–50	5·43 (0·20)	5·34 (0·39)	5·51 (0·28)

EDD=Estimated date of delivery.
*Group B *v* group C, $p<0·001$.

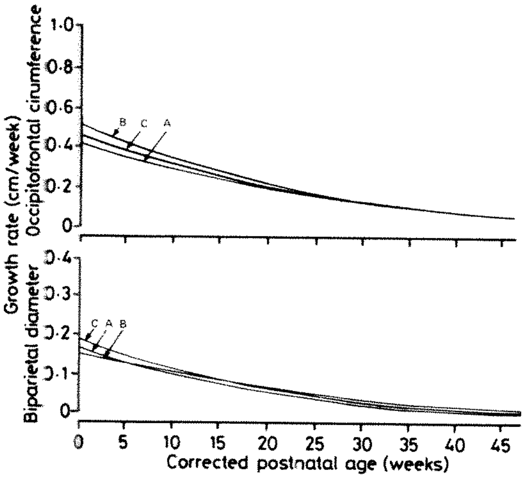

Fig. *Growth rate (cm/wk) in occipitofrontal circumference and biparietal diameter in infants in groups A, B, and C.*

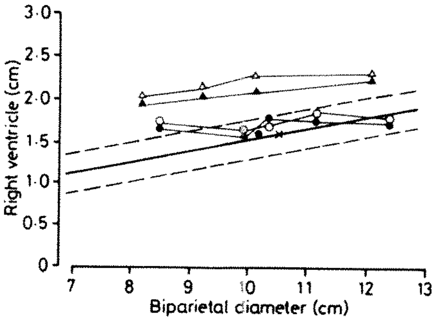

Fig. 2 *Width of the right ventricle in relation to the biparietal diameter. The regression line (———) and 95% confidence limits (- - - - -) drawn through 190 observations in 52 infants from the control group, group C (see text). Growth curves for two infants from group B: right (△) and left (▲) ventricles in case 1 (persistent ventricular dilatation); right (○) and left (●) ventricles in case 2 (transient ventricular dilatation).*

Ventricle size in relation to biparietal diameter. The relation of ventricle size to biparietal diameter was highly significant in infants in group C (190 observations in 52 infants), and this relation was identical for the right and left ventricles (right ventricle=0·127 biparietal diameter+0·214, $r=0{\cdot}98$, $p<0{\cdot}001$; left ventricle=0·122 biparietal diameter+0·271, $r=0{\cdot}98$, $p<0{\cdot}001$). Infants in groups A and C had a similar ventricle/biparietal diameter relation. Figure 2 shows the regression line and 95% confidence limits drawn through 190 observations on size of right ventricle in infants in group C. This Figure also shows growth curves of the right and left ventricles in two infants from group B (PVH + ventricular dilatation). One growth curve shows persistent ventricular dilatation and the other shows progress to a ventricle/biparietal diameter relation consistent with control values. Of the 26 infants in group B who started off with ventricular dilatation in the neonatal period, 18 showed progress to a ventricle/biparietal diameter relation consistent with controls (transient dilatation), while the remaining eight remained persistently dilated.

In the paragraph above the ventricle size has been related to head growth as measured by the biparietal diameter (Fig. 2). There were eight infants who showed persistent ventricular dilatation. In contrast, if the corresponding Figure is produced using 'the

Table 3 *Outcome in later childhood of the 98 infants studied*

Outcome	*Group A (PVH alone; n=20)*	*Group B (PVH and ventricular dilatation; n=26)*		*Group C (normal controls; n=52)*
		Transient (n=18)	*Persistent (n=8)*	
Normal	19	15	1	50
Developmental delay (developmental quotient <80)	1	3	7	2
Neurological abnormality:				
Cerebral diplegia	0	2	1	0
Athetoid	0	0	6	0
Fits	0	2	5	0
Partial blindness from retrolental fibroplasia	0	0	2	0
Sensorineural deafness	0	0	1	0

Levels of significance by Fisher's exact test for frequency of developmental delay or neurological abnormality: Group A *v* group C: not significant; Group B *v* group C: $p<0{\cdot}001$; Group A *v* group B: $p<0{\cdot}01$; Group B, transient *v* persistent: $p<0{\cdot}02$.
Transient or persistent ventricular dilatation in relation to biparietal diameter.
Normal developmental quotient >80 and no neurological abnormality.

age after estimated date of delivery' instead of the biparietal diameter on the horizontal axis only six infants are found to have persistent ventricular dilatation (the ventricle size always remaining greater than two standard deviations above the mean for controls). These latter six infants, identified on the age graph, were a subset of the eight infants identified on the biparietal diameter figure.

Outcome in later childhood. Table 3 shows that infants in group A did as well in their development as infants in group C and had a similar neurological state. Infants in group B had a worse outcome, but much of this could be attributed to a subgroup of eight infants with persistent ventricular dilatation: seven of these infants had developmental delay or a neurological abnormality, which was mostly due to the athetoid type of cerebral palsy. The remaining 18 infants with a later ventricle/biparietal diameter relation consistent with controls generally had a favourable outcome, apart from three infants with developmental delay or cerebral diplegia.

Discussion

In clinical practice measurements of head size give some indication of brain growth. In our study the initial 16 week period (after the estimated date of delivery) of fairly rapid growth in occipitofrontal circumference and biparietal diameter might be part of catch up growth previously observed in similar preterm infants, after body weight deficits in the neonatal period associated with various illnesses and feeding difficulties.[11] Indeed, during the catch up period head growth might be preferentially enhanced compared with bodily growth[12] but should not be mistaken for hydrocephalus. In the present study PVH does not seem to have had a significant effect on subsequent brain growth, judging by measurements of occipitofrontal circumference and biparietal diameter, although the measurements were misleading in eight infants for ventricular dilatation was not reflected in external dimensions of the head. The persistently dilated ventricles in relation to biparietal diameter in these infants possibly indicates brain atrophy.

It is known that the shape of the head alters after birth, since side to side flattening of the skull may take place due to the head lying on one side and then on the other.[13] As a result there is an apparent change in head configuration from a near circular to an elliptical one,[13] and we thought that this might influence the dimensions of the ventricles and brain hemispheres. The close correlations between the width of the lateral ventricles and the biparietal diameter suggest that both variables change at a similar rate during growth. This makes it possible to calculate the size of normal ventricles if the biparietal diameter is known, by using our predictive equations. In addition, it should be possible to monitor changes in ventricle size after PVH in relation to biparietal diameter by using Figure 2.

The static image (grey scale) ultrasound scanner used in this study is an instrument that is commonly used in obstetrics for measurements of fetal biparietal diameter. The accuracy of echo encephalographic measurements of brain ventricles with this technique has been previously established.[14 15] There is a close correlation between ventricle size measured by static image ultrasound and by computed tomography; also the severity of hydrocephalus indicated by computed tomography is in agreement with that indicated by ultrasound.[9] A sharp outline of the lateral margin of the ventricles was clearly visible by ultrasound due to differences in acoustic impedance between brain and cerebrospinal fluid. The images seen of the mid-body of the lateral ventricle, a sharp outline of the lateral margin, a midline echo thought to be generated by the septum pellucidum, and a strong echo from the inner surface of the skull, enabled us to carry out accurate measurements. We found it difficult to obtain reproducible measurements with similar accuracy of the transaxial plane with a real time sector scanner.

In relating ultrasound appearances of the brain to later outcome we have shown that the predictive value of neonatal scans can be improved by further ultrasound observations in the first year. When used on an outpatient basis the ultrasound caused little disturbance to the infants, spontaneous activity in infants did not affect the quality of imaging, and sedation was not necessary. Transient ventricular dilatation has previously been reported using real time ultrasound in four (26%) of 15 infants with dilated ventricles, after scanning repeatedly for 30 days postnatally,[7] and eight (38%) of 21 infants with dilated ventricles who had scans until discharge from hospital.[5] In both these studies the greater proportion of infants had persistent ventricular dilatation from an assessment based on a fairly short period. In comparison, in our study most dilated ventricles in our infants in group B reverted to normal size after 12 months' observations. On this basis 'transient' ventricular dilatation occurred in 18 (70%) of the 26 infants in group B when the size of the ventricle was assessed in relation to biparietal diameter or in 20 (77%) infants when the assessment was according to age after estimated date of delivery. Clearly, it takes a longer time for blood in the ventricles to be absorbed in order that ventricle size can revert to normal.

Early ultrasound findings in our study (Table 2) suggest that brain tissue was squeezed by distended ventricles against the inner surface of the skull. Our conclusion comes from the fact that all three groups have the same biparietal diameter, occipitofrontal circumference, and left and right hemispheres, but the ventricle size in group B is clearly increased. Thus if the skull size is fixed the brain must be squeezed when enlarged ventricles are present. This raises a possibility that the immature brain, which is known to contain less myelin, can to some extent accommodate distended ventricles by reducing its relatively large extracellular space. Unfortunately, by relating ventricle size to biparietal diameter in early infancy we cannot be certain whether the brain is merely being squeezed by distended ventricles, with a later possibility of recovery, or whether progressive brain atrophy is taking place. Measurements of head size or rates of head growth are not helpful in distinguishing between the two. Moreover, there is some uncertainty on our part about the reliability of intracranial pressure measurements, using non-invasive techniques, presently available in excluding brain atrophy. As the limitations of these methods in assessing prognosis in early infancy are recognised a more recent approach has been to investigate neonatal brains for periventricular infarction.

Infants with persistent ventricular dilatation may have included those with brain atrophy due to periventricular infarction, which is subsequently associated with retarded development and cerebral palsy.[16] [17] Volpe *et al* have shown by positron emission tomography that periventricular infarction can be more extensive than the haemorrhage suggests.[18] Recently, periventricular infarction has been diagnosed by real time ultrasound using a 7·5 mHz transducer, which provides better resolution.[19] [20] Extension of intraventricular haemorrhage into brain tissue carries a higher risk of major disability, and because of this the outlook after intracranial extension has been regarded with considerable pessimism, notably in very premature infants.[21] The three infants in our study with an intracerebral extension of haemorrhage had, indeed, persistently dilated ventricles and a poor outcome due to developmental delay and cerebral palsy. Thus in assessing outcome after PVH the relation of ventricle size to biparietal diameter at follow up should be used as a prognostic indicator.

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Sonographic finding of the bright thalamus

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SUMMARY Six of 83 asphyxiated neonates showed a diffuse increase of echodensity in bilateral thalami with or without other lesions in the basal ganglia on sonographic examination. The thalamic image still had a fairly high echogenecity compared with the surrounding brain parenchyma on follow up examination and was hence termed the bright thalamus. These six patients had a poor neurological outcome, including psychomotor retardation, spastic diplegia or quadriplegia, microcephaly, failure to thrive, seizures, and one death. The bright thalamus is not an occasional or an isolated sonographic finding of hypoxic-ischaemic encephalopathy, but it may serve as a landmark of severe hypoxic brain damage with adverse outcome.

Neonatal asphyxia is one of the main problems occurring in neonatal intensive care units. Brain insult during the neonatal period accounts for the adverse neurological outcome in many handicapped children with non-progressive neurological deficits.[1] The introduction of sector sonography provides an efficient, non-invasive diagnostic technique to evaluate these asphyxiated neonates at the bedside, even if the subject is being mechanically ventilated. The sonographic findings of post-asphyxial encephalopathy have been described by several authors.[2–4] An additional finding of hyperechodense bilateral thalami has been reported by one of us.[5] This finding had been termed the 'bright thalamus'. To clarify this finding and its prognostic value, the sonographic features of six cases with bright thalamus are presented and their clinical features as well as short term outcome are described.

Patients and methods

Eighty three patients with fetal distress or perinatal asphyxia were admitted to the neonatal intensive care units of our hospital from October 1983 to September 1985. All of them received sonographic examination of the brain either once or sequentially over an indefinite period. Perinatal asphyxia was defined according to the criteria of Mulliga *et al* and Finer *et al.*[6 7] Timing of the examination was decided by the attending physician according to the clinical state of the patient. The sonographic scanning was performed by the physician subspecialised in paediatric neurology and brain sonography. Since the first report of high amplitude echogenecity of bilateral thalami in our unit,[5] we have paid much more attention to the thalamic image obtained by sonography of asphyxiated neonates. Thus we have collected six cases with this finding in the past two years. We present here the study of these cases with their clinical manifestations, sonographic findings, results of computed tomography, and short term outcome.

Brain sonography was performed with the Aloka SSD-720 5·0 MHz sector scanner in both coronal and sagittal plane through the anterior fontanelle approach.

Computed tomograms were obtained in five cases, using a Toshiba TCT 80A and scan times of 2·7 seconds.

Results

The summary of clinical information and computed tomogram and sonographic findings of the six cases with bright thalamus are presented in the Table. All of the subjects were born at term with profound perinatal asphyxia. The delay of initial crying ranged from 10 to 20 minutes, with a mean of 16·3 minutes.

All six cases showed clinical features of hypoxic-ischaemic encephalopathy with seizures, disturbance of level of consciousness, and hypotonia or hypertonia during the neonatal period.

Timing of detection of the bright thalamus varied from 4 days to 4 months. One case, who had had serial scanning follow up since birth, had a bright thalamus image detected at 89 hours of age.

Table 1 *Summary of clinical, sonographic, and computed tomogram findings of six cases with the bright thalamus*

Case No	*Sex*	*Birth weight (g)*	*Gestational age (weeks)*	*Clinical presentation*	*Sonographic findings (age at findings)*	*Computed tomogram findings (age at findings)*	*Outcome (age)*
1	M	3400	40	DOIC 15 min; seizure; hypotonia; SIADH	High echogenetic thalami; basal ganglia (15d; 3·5 m)	Dilatation of lateral ventricles and basal cisterna; isodense thalami (25 d)	Psychomotor retardation; microcephaly; spastic diplegia (13 m)
2	F	2350	40	Fetal distress; meconium stain; DOIC 20 min; hypertonia; opisthotonos	Ventricular dilatation; high echogenetic thalami (4 m; 5·5 m; 7·5 m)	Ventricular dilatation; slightly hyperdense thalami (5·5 m)	Seizure; spastic quadriplegia; microcephaly (18 m)
3	F	3400	42	Meconium aspiration; DOIC 15 min; seizure; hypertonia	High echogenetic thalami; basal ganglia (3 d; 7 m)	Brain oedema; slightly hypodense thalami (7 d)	Microcephaly; infantile spasm (10 m)
4	M	3900	40	DOIC 15 min; seizure; hypertonia; acute renal failure	Brain oedema; high echogenetic thalami (89 h, 1 h after death)	—	Died (8 d)
5	F	1960	38	DOIC 15 min; seizure; hypotonia	High echogenetic thalami; basal ganglia (3 m; 6 m)	Multiple infarction, involving basal ganglia, thalami, and periventricular white matter (6 m)	Failure to thrive; psychomotor retardation; infantile spasm (8 m)
6	F	3500	41	Fetal distress, meconium stain; DOIC 18 min; seizure; hypotonia; SIADH	High echogenetic thalami; periventricular hyperechodense (7 d; 1 m) High echogenetic thalami; multicystic leucomalacia (3 m; 4 m)	Periventricular leucomalacia; slightly hyperdense thalami (1 m)	Psychomotor retardation; microcephaly; spastic quadriplegia; infantile spasm (4 m; 8 m)

DOIC=Delay of initial crying; SIADH=syndrome of inappropriate antidiuretic hormone secretion.

He died at the age of 8 days. The sonography was performed again one hour after death and showed mild obliteration of the hyperechoes. Unfortunately, we failed to obtain permission for autopsy from the parents. The other five cases received sonography follow up and showed persistence of hyperdense thalamus at the age of 3, 3, 3½, 6, and 7 months, respectively (Fig. 1).

Computed tomography was performed in the five remaining cases within 10 days after sonographic examination and all showed isodense or slightly hyper- or hypodense thalami (Fig. 2).

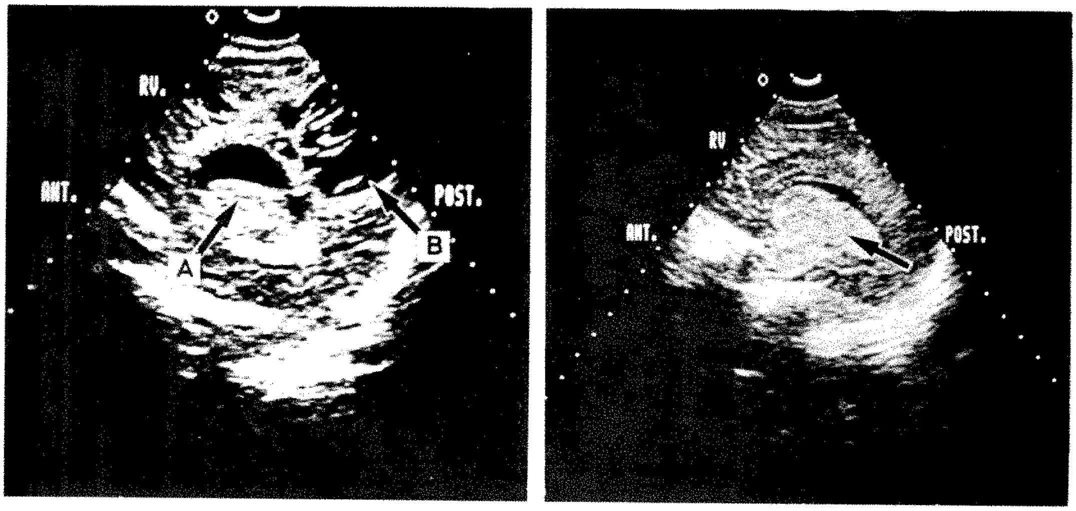

Fig. 1 *The bright thalamus. (a) Increased echogenecity of thalamus (A) associated with multicystic periventricular leucomalacia (B). (b) Diffuse echogenecity of thalamus and caudate nucleus (arrow).*

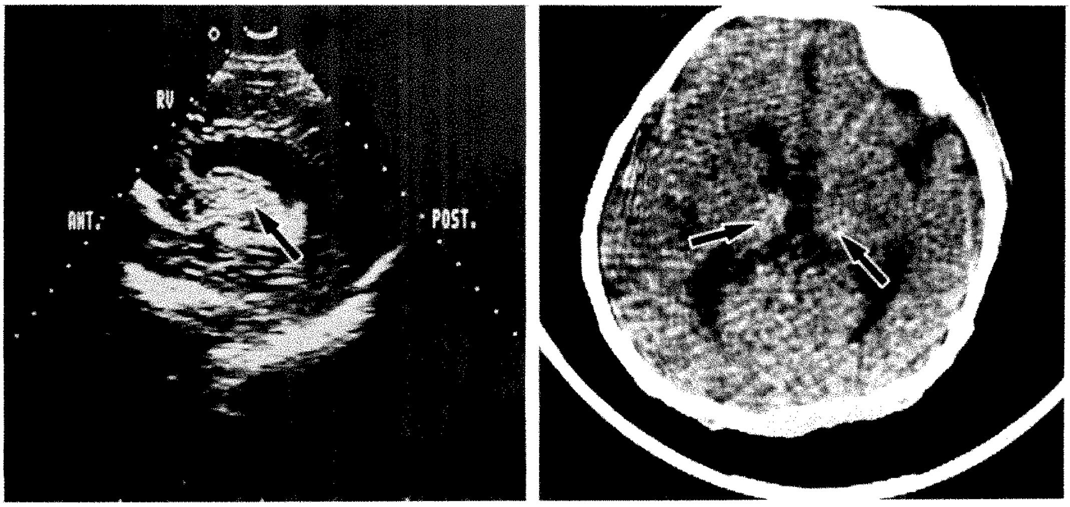

Fig. 2 *Case 2. (a) High echogenecity of the bright thalamus in the angle sagittal plane at the age of 5½ months (arrow). (b) Computed tomogram performed at the same time, showing slight hyperdensity of the thalami (arrow).*

Discussion

In normal sonography of the neonatal brain the thalamus appears as areas of medium level echogenecity.[8-10] The present study showed a diffuse increase of echogenecity over bilateral thalami in severely asphyxiated infants, and this image persisted on follow up sonography if the patient survived. We believe this may be a pathological feature of hypoxic-ischaemic encephalopathy because it was not found in our previous experience when examining 500 normal Chinese neonates,[11] 210 premature Chinese neonates (when attempting to determine the incidence of subependymal/intraventricular haemorrhage in premature Chinese infants. Unpublished data.), and more than 1200 scans of sick infants who were not asphyxiated.

Previous investigators have succeeded in detecting parenchymal echogenecity in the neonatal brain with post-asphyxial encephalopathy.[2-4] They suggested that the hyperechogenecity was presumably due to widespread ischaemic change, cerebral oedema, or focal ischaemia in the distribution of one of the major cerebral vessels.[4]

Skeffington *et al* reported 13 cases of perinatal asphyxia with diffuse high amplitude echogenecity throughout the brain and suggested cerebral oedema.[12] Others have described an echogenic appearance that corresponded to brain oedema during an intraoperative procedure.[13 14]

In the present six cases two who had been given a sonographic examination in the early neonatal period showed diffuse increase of echogenecity in whole brain parenchyma and obscured the echoes of normal structures as described by Skeffington *et al.*[12] The high amplitude echoes attenuated with time, but the thalamic echoes gradually became more obvious. The computed tomograms remained isodense or slightly hypodense compared with other brain parenchyma (Fig. 2). They became slightly hyperdense if the scanning was performed in late infancy.

Primary thalamic haemorrhage is a rare finding during the neonatal period.[15-17] It may mimic the bright thalamus sonographically. An early computed tomogram may differentiate the bright thalamus from the thalamic haemorrhage by the higher resolution density on the scan of the haemorrhage. From the sonographic point of view, the bright thalamus showed a diffuse homogenous echogenecity all over the thalamus and the margin was sharp and regular. A previous report of acute haemorrhagic necrosis of the thalamus and basal ganglia with neuropathological confirmation showed the striking feature of haemorrhage with strong echogenecity and irregularity of the echoic margin.[15] The primary thalamic haemorrhage reported by Trounce *et al* also showed heterogenous echoes of the haemorrhage.[16] The bright thalamus tends to be a diffuse parenchymal change of the thalamus rather than a focal destructive lesion.

Hypoxic-ischaemic insults may cause diffuse brain damage, in particular to the cerebral cortex, subcortical and periventricular white matter, basal ganglia, brain stem, and cerebellum.[18,19] The thalamus is one of the nervous tissues most vulnerable to hypoxia. Sensory nuclei, including the thalamus, lateral geniculate body, and colliculi, are the subcortical structures that bear the brunt of asphyxic brain damage because of their high metabolic requirement.[18] Rorke suggested that selective damage to thalamus or deep grey nuclei, or both, probably results from diminution of blood flow in branches of basal penetrating vessels or from the phenomenon of selective neuronal vulnerability.[19]

Sonographically, the bright thalamus was just one feature of hypoxic-ischaemic encephalopathy in our cases. Increased echoes of the basal ganglia (cases 1, 3, and 5) and parenchymal change, such as multicystic periventricular leucomalacia (case 6), were also noted. Whether there is any lesion in the brain stem or cerebellum is difficult to ascertain due to the limited resolution of the machine. The outstanding thalamic echogenecity is, however, much more easily identified than others. Thus it may represent a critical sign of hypoxic brain insult.

The neuropathology of the persistence of the bright thalamus in late infancy remains obscure. We presume this could be a feature of status marmoratus and look forward to a pathological confirmation. This disorder is more common in term than in premature infants, with premature birth being noted in fewer than 5% of cases.[20,21] The neurological manifestations of status marmoratus in the neonatal period are unknown.[1] A further study of the correlation between the bright thalamus and status marmoratus will be helpful in identifying this disorder early.

Five of our cases survived and all showed pronounced psychomotor retardation and other complications, such as microcephaly, seizures, spastic diplegia or quadriplegia, and failure to thrive. The thalamic damage per se may not account for all of these complications. From the present study, we found that only 7% (6/83) of the asphyxiated neonates had such complications, and all of them had longer duration of asphyxia than others. This suggests that the bright thalamus is only found in profoundly asphyxiated neonates.

In summary, the bright thalamus should be distinguished from thalamic haemorrhage or other thalamic desease. It is not an occasional or an isolated finding in hypoxic-ischaemic encephalopathy. The association of increased echogenecity of the basal ganglia or other parts of the brain is not rare. But because of its easy identification, we suggest that the bright thalamus may serve as a landmark of profound asphyxic brain damage with adverse neurological outcome.

We thank the sisters and nursing staff of the neonatal intensive care units for their help and cooperation and Miss H J Chang for technical help.

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Age specific xerophthalmia rates among displaced Ethiopians

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SUMMARY The recent famine in Ethiopia has resulted in the dislocation of millions of people. Many of these individuals have moved to refugee camps in Sudan or to feeding centres within Ethiopia.

A total of 1325 children up to the age of 15 years were examined by an ophthalmologist in January 1985 at several sites in these two countries. The rates of Bitot's spots were three times greater in those between the ages of 7 and 10 compared with those under 7. Rates of corneal xerosis were comparable for each group. Previously, xerophthalmia was considered predominantly to affect children aged under 6. These data document the presence of the disease in older children and raise questions regarding future modifications in the prevention and treatment of xerophthalmia.

Xerophthalmia has been recognised as one of the leading causes of childhood blindness in most developing countries.[1] Initially found in high rates in Asia, recent reports clearly show considerable problems with vitamin A deficiency on the African continent.[2 3] The presence of large numbers of children in areas of drought and political upheaval has resulted in mass starvation and attendant to that some of the highest rates of xerophthalmia ever recorded.[4]

Traditionally, xerophthalmia has been considered to have peak prevalence in children 2–6 years of age.[5] Because of the severity of the nutritional situation in Ethiopia, all children up to 14 were considered at high risk for malnutrition and so were included in this assessment.

Patients and methods

In January 1985 a rapid assessment was carried out to determine the extent of xerophthalmia among children from birth to 14 years of age who were affected by the recent drought in Ethiopia. Children were seen at several sites, located at two refugee centres in the Sudan that housed Ethiopians as well as at feeding centres within Ethiopia itself. Transport limitations necessitated that only these areas were visited. At each site children were sampled from as many different settings as possible to broaden the representation of the population at risk. All children had been subjected to severe deprivation and starvation in the preceding months.

An ophthalmologist (LDP) saw each child, asking for age and sex, and then, using a handlight, examined the ocular adnexa, conjunctiva, cornea, and anterior chamber. Visual acuity was estimated to be better or worse than 3/60 based on clinical signs. Whenever possible, children with appreciable corneal scarring or blindness were examined as thoroughly as possible, given the field conditions. Any informant present with the child was queried concerning clinical history, and every attempt was made to assign an aetiology to each case of important ocular disease. Children with any signs of active xerophthalmia were treated appropriately.

Results

Children were examined at several sites in both countries, as summarised in Table 1. The subsites where the assessment was performed are listed as

Table 1 *Children examined categorised by site*

Site	*Type*	*Population*	*No of children examined*
Wad, Kowli, Sudan	Refugee camp	50 000	518
Wad Sheriffe, Sudan	Refugee camp	80 000	166
Alamata, Ethiopia	Feeding centres	Not applicable	641

well as the population of the sites at the time of the assessment and the nature of the setting.

A total of 1325 children was examined for whom age and sex were available, and the information is given in Table 2. Sixty four cases of xerophthalmia in any of its manifestations, except night blindness, were found, giving an overall rate of 4·8%. The age specific rates for the various manifestations of xerophthalmia for each site are given in Tables 3–5.

Table 2 *Children examined categorised by age and sex*

Age (years)	*Boys*	*Girls*	*Total*
0–1	55	49	104
2	80	88	168
3	64	57	121
4	64	66	130
5	66	64	130
6	59	38	97
7	66	51	117
8	60	49	109
9	42	33	75
10	96	74	170
11	11	12	23
12	31	11	42
13	13	6	19
14	12	8	20
Total	719	606	1325

Table 3 *No of cases (rate/1000) of Bitot's spots categorised by age and sex*

Age (years)	*Boys*	*Girls*	*Total*
0–6	5 (12·9)	2 (5·5)	7 (9·3)
7–14	14 (42·9)	5 (20·7)	19 (33·5)
All	19 (26·6)	7 (11·6)	26 (19·7)

Table 4 *No of cases (rate/1000) of corneal xerosis categorised by sex and age*

Age (years)	Boys	Girls	Total
0–6	3 (7·7)	8 (22·1)	11 (14·7)
7–14	4 (12·3)	2 (8·3)	6 (10·6)
All	7 (9·8)	10 (16·5)	17 (12·9)

Table 5 *Other cases of xerophthalmia than those listed in Table 4 categorised by age and sex*

Age (years)	*Corneal scars*	*Phthisis bulbi*	*Kerato-malacia*	*Blind* second degree xerophthalmia*
0–6	3	1	5	3
7–14	8	2	2	3
All	11	3	7	6

*Includes those already appearing in this Table.

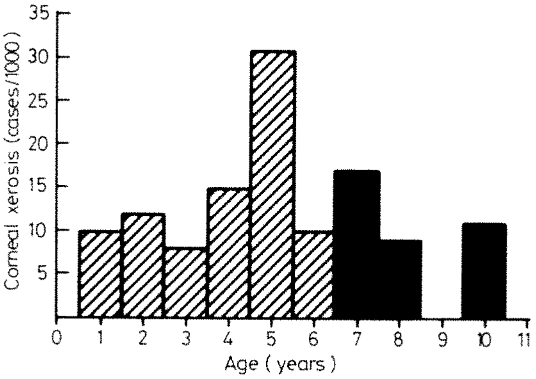

Fig. 1 *Age specific rates of Bitot's spots per thousand for the population studied.*

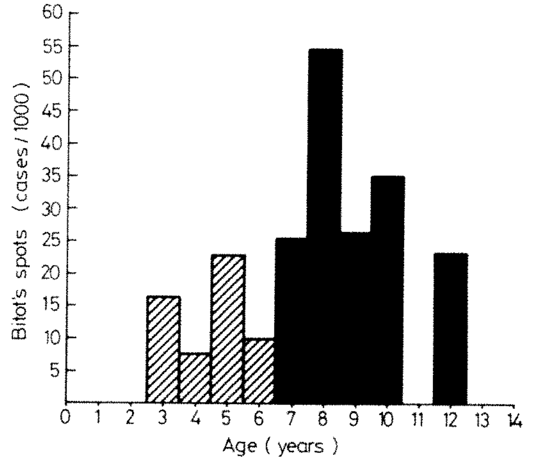

Fig. 2 *Age specific rates of corneal xerosis per thousand for the population studied.*

The ages were combined into two groups, 0·6 years and 7–14 years, for ease of comparison and to improve accuracy in age reporting as well as analysis.

The χ^2 test was used to evaluate the significance between age groups for each condition (for either condition there was no significant difference between sex). Figures 1 and 2 show the age specific rates for Bitot's spots and corneal xerophthalmia for the entire population examined.

Discussion

The recent famine has had a devastating effect on the people of northern Ethiopia. The resultant malnutrition has been as bad or worse as any seen previously. One would expect all nutritional deficiency diseases, particularly vitamin A deficiency, to be found in high rates in this population. Clearly, this has been the case as has been reported and can be seen in these results. Overall, 4·8% of the population studied (children from birth to 14 years of age) had some clinical signs of xerophthalmia. This is greater than rates seen in previous refugee populations[6] and is as high or higher than those rates seen in previous prevalence surveys in Asia.[2 7 8]

Xerophthalmia prevalence surveys performed recently have tended to be limited to children aged under 7. The World Health Organisation guidelines for control of xerophthalmia state that children aged under 6 are most at risk for developing the disease and therefore suggest concentrating on this age group during assessments. Various authors have reported peak rates of corneal xeroses and Bitot's spots in 3 to 4 year olds, with a drop off in rates after the age of 5. Solan *et al*, however, reported persistence of the signs of active xerophthalmia in all age groups up to 16 in the Philippines.[2] Similar data have been gathered in Bangladesh.[3]

Sommer, in an exhaustive study in Indonesia, has found that while Bitot's spots may be seen in children over 6, the percentage of these lesions that do not respond to administration of vitamin A rises rapidly.[7] These so called 'vitamin A resistant' Bitot's spots may not represent a manifestation of the deficiency.

Because of the extreme degree of global malnutrition in the Ethiopian situation, I elected to examine all children up to 14 years of age. The circumstances in which this assessment was performed were not conducive to rigorous sample selection. Refugee camps and feeding centres have population shifts on a daily basis. The need to feed thousands of individuals took precedence over any systematic registration or monitoring activities. Whenever possible, multiple examination sites were chosen in the various locations. All children were seen who were either living at or who had gathered at the examination site. No children were included who were receiving hospital care. Every effort was made to examine a representative sample of the population. The limitations of the sampling technique made stratification impossible; the data do show consistent trends, however, in prevalence of xerophthalmia.

No demographic data existed for the population sampled. It would be expected that a typical population pyramid in developing countries would have 35-50% of the population below 15. High child mortality in this population may have altered that rule. More children aged under 6 were examined (750) than those aged 7 and over (567). Boys comprised 54% of those examined, which may represent a bias toward male preservation in such a dramatic situation. Age was provided by the parent or guardian when available or by the examinee in older age groups. There were no documents available to verify age, and clearly some rounding off of age does occur, as seen by a large cluster of children aged 10, with fewer at 9 and 11 years. Any gross discrepancies between stated age and appearance of the child led to more extensive questioning and attempts to assign age more accurately.

Age specific rates for Bitot's spots show a pronounced shift toward older age groups (Fig. 1). The peak prevalence occurs at 8 years, with a greater than threefold increase in prevalence for those 7 and older compared with the younger group, a difference that was significant to the $p<0{\cdot}01$ level. Conceivably, some of these cases may not be related to xerophthalmia, yet even allowing for these, many Bitot's spots related to xerophthalmia would be found in this group. The rates for corneal xerosis show considerably less of the shift to older ages (Fig. 2). The ratio of corneal xerosis prevalence for those aged ≤ 6 compared with those >6 is 1·4:1. One third of the cases of corneal xerosis seen would have been missed if those aged 7 and over had not been examined. Statistical evaluation by χ^2 test of these data showed no significant difference in the rates between the two age groups for either sex. Relatively few children between the ages of 11 and 14 were seen. The cases of xerophthalmia in this group, therefore, can yield dramatically high prevalences for these age groups. It can be said that cases of xerophthalmia were seen in this group over 10, but the true significance of this problem remains for further elucidation.

The other clinical manifestations of xerophthalmia were seen less often (Table 3–5). Eleven corneal scars compatible with xerophthalmia were seen, eight of them in children aged over 7. Phthisis bulbi was evident in three cases, two of whom were aged over 7. Active keratomalacia, rarely seen in a prevalence survey, was present in seven children, five of whom were aged 6 or less. Six children were blind from presumed xerophthalmia, three in each age group.

The tragedy of Ethiopia has an added dimension of childhood blindness caused by xerophthalmia. This blindness remains preventable if massive doses of vitamin A supplementation can take place. Such a distribution was begun in Ethiopia and Sudan in 1985, in large part based on this assessment. Inclusion of children up to the age of 14 resulted in recognition of many active cases of xerophthalmia and some potentially blinding ones. It seems appropriate to alter the guidelines for treating xerophthalmia, particularly in drastic situations like the case in Ethiopia, to include children at least to age 10 in both assessment and prevention activities.

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British Paediatric Association

Annual meetings

At York University:
1987 April 7–10
1988 April 12–16
1989 April 11–15

At University of Warwick:
1990 April 3–7
1991 April 16–20
1992 April 7–11
1993 April 19–23 (provisional)
1994 April 11–15 (provisional)

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DDAVP and urine osmolality in refractory enuresis

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SUMMARY A double blind crossover trial of 20 µg intranasal 1-deamino-8-D-arginine vasopressin (DDAVP) versus placebo was carried out in 17 children with intractable enuresis aged between 6 and 13 years who had failed to respond to drugs and an enuresis alarm. Fluid intake was not restricted. There was a significant reduction in the number of wet nights. Seven children (41%) were cured or showed considerable improvement, with strong evidence against any placebo effect. The best response was seen in children aged 10 years or over and if urine osmolality after DDAVP reached beyond 1000 mmol/kg or was already at this concentration. The degree of overnight rise in urine osmolality after treatment with DDAVP was not predictable but correlated well with the clinical improvement in nocturnal diuresis present in eight of the children.

A further 12 children with equally refractory enuresis were given 20 µg of the active drug to take during their school journeys or holidays. Six of them had previously normal overnight urine osmolalities with only two successes, but of the six who had nocturnal diuresis before treatment, five became dry, suggesting that DDAVP acts largely by anti-diuresis and might be most useful in children with nocturnal polyuria.

Intranasal 1-deamino-8-D-arginine vasopressin (DDAVP), the synthetic analogue of vasopressin, is the treatment of choice for diabetes insipidus that is sensitive to vasopressin because it has a prolonged anti-diuretic action dependent on dose with no side effects[1 2] nor inhibition of growth hormone, prolactin, or cortisol at night in children.[2]

Could nocturnal enuresis be helped by this anti-diuresis? In a pilot study 10 µg of intranasal DDAVP was effective in 11 of 20 children with resistant enuresis.[3] This was confirmed with 10–40 µg both in controlled studies[4–6] and double blind clinical trials,[7–12] with but one dissent.[13] But in many of these studies an enuresis alarm (the 'buzzer') had never been used and the degree of enuresis was not severe. In diabetes insipidus there is a consistent and considerable rise in urine osmolality after treatment with DDAVP, but there has been no such detailed study of this topic in enuresis. A double blind trial with crossover was therefore designed not only to determine the value of 20 µg DDAVP in enuresis refractory to conventional treatment, including the buzzer, but more importantly to see whether a rise in urine osmolality was a necessary factor in any success achieved.

Patients and methods

Some 200 children attend a community health enuretic clinic in Woolwich (south east London). Seventeen (14 boys and three girls) between the ages of 6 and 13 years were selected because, like those in the pilot study, they had failed to respond to treatment with drugs (mainly imipramine and amitriptyline) and the buzzer over a mean period of two years. Eight had been wet every night (many twice or more), but two had once been dry between 2 and 3½/4 years of age. Informed consent was obtained from their mothers. Children were excluded from the trial if they had more dry nights than wet in the observation period of two weeks or if they had a urinary infection or showed any clinical or radiological evidence of organic disease. As with all children with enuresis their homes had been visited by a social worker, usually the one attached to the clinic, who found that 10, including three with secondary soiling, came from broken homes. Most were psychologically disturbed.

Every child was allocated randomly to take intranasally either 20 µg DDAVP or a seemingly identical placebo. Neither the parent nor the doctor knew the code. The clinic sister patiently showed each child how to blow the liquid up his nose using a graduated plastic tube (rhinyle). At each bedtime, for two weeks, the bladder was emptied and the liquid instilled. This was immediately followed for the next fortnight by the other solution. After each period the child had to produce his empty phial. No other treatment was given during the trial and fluids were not limited. The number of wet and dry nights were charted for each period. The first urine sample to be tested for osmolality was passed in the afternoon at the clinic immediately before the trial and the second and third were collected after each fortnightly period on waking. Urine osmolality was determined by depression of the freezing point using an MSE osmometer (maximum reading 1400 mmol/kg) Weight and blood pressure were measured before the trial and at the end of each period. The child was also weighed at school between clinic visits. Serum osmolality was not estimated because venepuncture was considered a 'minimal risk procedure'. Unless otherwise indicated, the results were analysed by the Fisher exact single tail method.

Results

Clinical. There were no side effects and there was no clinical evidence of overhydration and no significant change in blood pressure or body weight.

Overall, treatment with DDAVP produced a significant clinical improvement, with 117 wet nights in two weeks against 169 on placebo ($p<0\cdot02$ by the Wilcoxon method for ranked paired data). Two children showed complete cure during the treatment with DDAVP (all nights dry), five were greatly improved (at least five dry nights a week), five were slightly improved (averaging three dry nights a week, one night more than with placebo), and five were failures, including three who became dry at the mother's bedtime and were less 'soaked' by morning. Thus treatment with DDAVP was successful in seven of the 17 children (41%). That these successes might have been due to a placebo effect was unlikely because there were no successes on placebo, only five improving slightly and the remainder being failures. Moreover, when the placebo was given first (10 cases) all but two (who failed clinically) of the children showed greater improvement when subsequently treated with DDAVP, whereas when the active drug was given first (seven cases) treatment with placebo showed greater improvement in only two (who were also failures).

No significant difference was found between children from intact and broken homes or between those who had and had not been wet every night. Older children, however, fared better than younger ones, with four successes in the six who were aged 10 years or more (56 dry nights in two weeks, mean 9·3) but only three in the 11 aged less than 10 (55 dry nights in two weeks, mean 5·9) ($\chi^2=12\cdot05$, $p<0\cdot001$).

Urine osmolality. The range of overnight urine osmolality in normal children is 873–1305 mmol/kg.[14] Osmolality was increased by treatment with DDAVP in all but five of the children. There was a clear and significant relation between osmolality and clinical response (Table 1). The best results were achieved if overnight urine osmolality after treatment with DDAVP increased beyond 1000 mmol/kg or if it was already at this concentration after treatment with placebo, which allowed little room for a further increase (four cases, comprising three successes and one failure). If urine osmolality failed to reach 1000 mmol/kg, however, results with one exception were poor ($p<0\cdot005$).

There were eight presumed cases of nocturnal water diuresis, who had an overnight urine osmolality of 250–505 mmol/kg, in contrast to the remaining nine, whose range was 745–1143 mmol/kg (Table 2).

Table 1 *Clinical results and concentrations of overnight urine osmolality reached after treatment with DDAVP*

Urine osmolality after DDAVP (mmol/kg)	*Successes*		*Failures*		*Total successes*
	All dry	*Greatly improved*	*Slightly improved*	*All wet*	
1041–1348	2	4	—	2	6/8
857–961			2	1	1/9
605–733		1	2	1	
240–373				2	
Total	2	5	4	6	7/17

Table 2 *Overnight urine osmolalities (mmol/kg) after treatment with placebo or DDAVP compared with afternoon osmolalities before trial*

	Urine osmolalities			*Results*
	After placebo	*After DDAVP*	*Afternoon*	
No nocturnal diuresis	1190	1112	1084	Great improvement
	1143	1348	980	Cure
	1086	1041	1051	Great improvement
	1004	1146	911	No improvement
	920	961	962	Slight improvement
	866	1050	1030	No improvement
	841	1019	1077	Cure
	841	733	837	Slight improvement
	745	676	458	Slight improvement
Nocturnal diuresis	505	605	920	No improvement
	498	1049	1167	Great improvement
	387	880	1098	Slight improvement
	330	857	316	No improvement
	325	240	817	No improvement
	310	373	491	No improvement
	269	642	704	Great improvement
	250	1044	966	Great improvement

Results:
Poor: No improvement=all nights wet.
Slight improvement=one night a week dry more than with placebo.
Very good: Great improvement=only one or two wet nights a week.
Cure=all nights dry.

Clinical results were good in three and four children from these two groups, respectively, but the five with nocturnal diuresis who gave poor results included two whose osmolalities were virtually unchanged after the drug from a base so low (310 and 325 mmol/kg, respectively, after placebo) that either DDAVP was not taken or not absorbed or else tubular function was so impaired by gross polydipsia as to render the drug useless. One of these two children was admitted to hospital for investigation and treatment with DDAVP; no abnormality was discovered and he was dry three nights out of four when receiving DDAVP so that it is probable that he was not taking it at home.

The most likely cause of nocturnal diuresis is compulsive drinking on the previous evening. This hypothesis is supported by the finding (Table 2) that in all eight cases the osmolalities in the afternoon before the trial began averaged 131% higher than that recorded in the urine specimens taken the first morning after placebo; this compares with only 2·5% higher in the nine cases in whom nocturia was absent.

Subsequent experience It was found that those who responded to treatment with DDAVP did so very quickly but relapsed when it was stopped. Its appropriate use would therefore apply to urgent situations such as school journeys and holidays.[3] During the three years since this trial was completed, therefore, 12 more children aged between 7 and 13 years with equally refractory enuresis have been given 20 μg DDAVP to take on such occasions. Before departure, overnight urine osmolalities were normal in six, but in the other six they were abnormally low (≤651 mmol/kg). Success was achieved in seven of the 12 (58%), five with nocturnal diuresis but only two with normal osmolalities. Four of the five successes with nocturnal diuresis were so delighted that they asked for DDAVP again for the same purpose (one had it three times and two twice) with the same improvement on each occasion, even though they relapsed soon afterwards. It was not practicable to estimate urine osmolality immediately after their return, but it is suggested that any benefit obtained was due to anti-diuresis.

Discussion

This double blind crossover trial shows the efficacy and safety of treatment with 20 μg DDAVP even in patients with intractable nocturnal enuresis, all of whom had failed to respond to drugs and the buzzer. Considerable improvement was obtained in almost half of these children (41%), with substantial evidence against a placebo effect. This overall figure does not differentiate, however, between the children with and without nocturnal polyuria. This distinction is admittedly based on only three tests of urine osmolality on different days but it proved impracticable to do more in a busy clinic remote from the local laboratory. This limitation, however, should not invalidate the overall conclusions.

Eight of these 17 children probably had nocturnal diuresis, given their low overnight urine osmolality (<505 mmol/kg) on placebo, which possibly correlated with compulsive drinking on the previous evening because of the significant difference between the fairly high urine osmolalities on the afternoon before the trial began and the low readings in the first morning urine samples after treatment with placebo. Such nocturnal polyuria was found in 27% of 240 unselected children with enuresis at this clinic (unpublished observation), in each of six children studied by Birkasova *et al*,[7] and in six of 11 children with enuresis who all showed abnormally low plasma anti-diuretic hormone concentrations during the night.[15]

In the present trial DDAVP seemed to be of equal value in cases with and without nocturnal diuresis, but only if the two failures with very low osmolalities after treatment with both drug and placebo are included.

Mode of action. Urine osmolality of over 1000 mmol/kg was a clear predictor of clinical efficacy. In the absence of nocturnal diuresis, however, the clinical failure in two children, despite a rise in osmolality of 14% and 21%, respectively, to this figure and the great improvement obtained without any rise at all in another two (Table 2), suggests that some other factor besides anti-diuresis may occasionally also be involved, such as improved memory and learning.[9] Nevertheless, a recent study supported anti-diuresis as the sole mechanism as treatment with DDAVP increased urine osmolality significantly, although no details were given.[16]

Some of the poor results may have been due to failure to take the drug or to inadequate absorption either from nasal congestion[11 12] or faulty technique, especially in younger children, some of whom felt fluid in the pharynx with consequent loss (one child said it 'tasted horrid'). The significantly better results in older children found in this and other series[9 10] may be attributed to better motivation and compliance with the technique, which, if not properly followed, would mean that an inadequate dose would be absorbed. It has been shown that the lower the dose the smaller and earlier the peak,[2] which is normally attained four to eight hours after an intake of 20 μg,[1] so that some children are wet only after midnight. Another but rare cause for failure is gross polydipsia, which alone[17] or combined with emotional stress[18] may inhibit the release of anti-diuretic hormone during the night when it normally increases by up to 140%;[19] the resultant transient nephrogenic diabetes insipidus cannot then respond to DDAVP. Such a cause could not be established in any child in this series.

Naturally, in any individual the degree of compulsive polydipsia, presumably psychogenic, is impossible to quantify as it is so often surreptitious. But even without polydipsia, nocturnal concentrations of anti-diuretic hormone have been found to be fairly low in children with enuresis[15] but sufficient to allow urinary output to exceed the functional capacity of the bladder. Unfortunately, DDAVP was not used in that study, but if low anti-diuretic hormone concentrations can be confirmed DDAVP might be regarded as replacement therapy.

Further study of the interaction between DDAVP, severe enuresis, nocturia, and compulsive polydipsia with larger numbers seems highly desirable.

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Nebulised beclomethasone dipropionate suspension

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SUMMARY We compared nebulised beclomethasone dipropionate suspension against placebo in 16 children with moderately severe asthma in double blind crossover fashion. Three children withdrew due to deterioration while on placebo. Of the remaining 13, eight were better on beclomethasone and five on placebo. These trends in favour of nebulised beclomethasone were not significant and do not suggest that the suspension is as effective as inhaled powder or aerosol topical steroid formulation.

The role of beclomethasone dipropionate in childhood asthma is well established, with proven clinical efficacy when administered by either metered dose inhaler[1] or powder capsule[2 3] form. Neither of these two delivery systems is suitable, however, for treatment of very young children, due to the degree of cooperation and coordination required in their use.

It is only fairly recently that a suspension form of beclomethasone, for delivery by nebuliser, has become available, but to date there is only one published clinical trial of its effectiveness in a suitable population of young children.[4] We have therefore conducted a randomised double blind crossover study, comparing beclomethasone dipropionate suspension against placebo in a group of children with moderately severe asthma aged between 18 months and 6 years.

Patients and methods

The age limits of 18 months and 6 years were chosen to include those children old enough to be responsive to treatment with bronchodilator[4] but too young to be able to manage treatment with rotahaler or metered dose aerosol effectively. All the children had an established clinical diagnosis of asthma and all had been considered to be inadequately controlled on regular nebulised sodium cromoglycate with nebulised bronchodilator as required.

After an initial two week run in period, during which regular prophylactic treatment was stopped, the patients entered two consecutive two month treatment periods. In each of these they received, through a Pari Inhalierboy nebuliser and face mask, either beclomethasone respirator suspension 150 µg (3 ml) or placebo 3 ml (the commercially available preparation minus the active ingredient) on a double blind, randomised crossover basis, and as the sole form of prophylactic treatment.

Throughout the trial the parents were asked to maintain a daily diary record of: (i) symptom score, allocating a score of 0–3 for each of cough, wheeze, and breathlessness for both day and night, giving a worst possible score of 18 for each 24 hours; (ii) morning and evening peak expiratory flow rate if the child was capable, using a Wright's Mini Peak Expiratory Flowmeter; (iii) the number of bronchodilator doses; (iv) any other medication required—for example, corticosteroids.

The children were seen as outpatients at monthly intervals during the trial, at which time they were examined and possible side effects of treatment sought.

Statistical methods employed were Wilcoxon's signed rank test, Fisher's exact test, and the Sign test.

Fully informed parental consent was obtained before entry into the trial, and the study was approved by the local ethical committee.

Results

Twenty children were entered into the study, but four were withdrawn and their results not analysed—one because of severe deterioration while off prophylactic treatment during the run in period, one due to non-compliance in diary recording, and two after the parents changed their mind after the run in period. Details of the 16 patients who entered the treatment periods are shown in Table 1.

Three children failed to complete the full double blind treatment period of four months. All three failures were due to appreciable deterioration in

Table 1 *Details of the 16 patients entering the treatment period*

	Mean (SD)	*Range*
Age (months)	40·9 (11·6)	23·6–59·8
Age at onset of asthma (months)	8·9 (8·9)	0–36
Duration of asthma (months)	32·1 (13·3)	12–58
Sex (male:female)		14:2
Personal history of:		
Eczema		7
Rhinitis		11
Allergies (skin)		6
Current treatment:		
Nebulised bronchodilator		16
Nebulised sodium cromoglycate		13
Inhaled steroid:		
Budesonide spacer		2
Nebulised beclomethasone		1
Oral corticosteroids (daily)		1
Previous treatment:		
Oral corticosteroids (courses)		13

control of asthma to the extent that the parents were understandably unwilling to continue treatment on a blind basis. Each child was on placebo at the time of deterioration, one in the first two months of treatment and the other two in the second.

Of the 13 patients who completed the trial, eight were considered by their parents to be better controlled while on nebulised beclomethasone (analysis of diary records supported their views), but five were considered to be better controlled on placebo. This difference was not significant using the relatively insensitive Sign test, but even if the three placebo treatment failures were included in the 'beclomethasone beneficial' group, the difference of 11 *v* 5 was only significant at the 25% level.

Analysis of the diary records had to be restricted to the 13 children who completed the trial. As can be seen from Table 2, there are no significant differences between the two treatment periods in terms of individual symptom and total symptom scores (similarly, there was no difference between treatments on daytime scores or night time scores). The number of extra bronchodilator doses required was similar in the two groups, and the number of children requiring a course of oral corticosteroid was identical. The one child on daily maintenance oral corticosteroid therapy consumed a total of 228 mg of prednisolone in the six weeks of treatment with placebo, but only marginally less (180 mg) while on nebulised beclomethasone.

Although the order of treatments was randomly determined, the distribution was uneven. Of all 16 patients, five were given beclomethasone first and 11 placebo first, with no significant order effect on the result (p=0·28, Fisher's exact test). In the 13 completed trials, however, three were given beclomethasone first and 10 placebo first, with an order effect that is almost significant at the 5% level in favour of beclomethasone (p=0·07, Fisher's exact test).

There was no discernable seasonal influence, there being an even distribution of treatment periods throughout the calendar months.

No side effects of treatment were detected clinically.

Discussion

This study has failed to show clear benefit from the use of nebulised beclomethasone dipropionate suspension in young chidren with moderately severe asthma. These results are quite at variance with similarly small studies using the metered dose inhaler[1] and powder capsule[2] delivery systems, which showed unequivocally improved asthma control, albeit in slightly older children who were able to use these devices. We do not therefore doubt the efficacy of the drug itself. Thus, if our results reflect a true picture, there must be three areas for further

Table 2 *Dairy records of 13 completed courses (analysis restricted to last six weeks of each treatment period)*

	Maximum	*Placebo*		*Beclomethasone*		*Wilcoxon*
		Median	*Range*	*Median*	*Range*	
Cough	252	73	1–142	90	2–149	NS
Wheeze	252	37	6–112	49	2–108	NS
Breathlessness	252	89	0–112	42	0–179	NS
Total score	756	182	8–312	182	4–395	NS
Symptom free days	42	2	39–0	5	40–0	NS
Bronchodilator doses		89	0–159	59	1–346	NS
Prednisolone:						
Short courses (No of children)		4		4		—
One child on daily treatment (mg total)		228		180		—
Admissions (No of children)		2 (× 3 admissions)		0		—

enquiry. Firstly, could it be some property of the physical suspension that makes it less effective (all other anti-asthma nebuliser preparations are in the form of a solution); secondly, could the physical characteristics of the suspension have affected nebuliser function, reducing its efficiency; and, thirdly, could the recommended dose simply be too low (most other nebuliser dosages are considerably higher than inhaler dosages, though the proportion of either that reaches the lungs is said to be similar at about 9–12%[5 6])? It is impractical to expect toddlers and young children to be able to tolerate a higher dose at each sitting as even the nebuliser time for 3 ml of suspension (50 mcg/ml) represented an appreciable burden to many of our parents and children.

Although no side effects were noted in our study, there is a theoretical risk of secondary steroid effects upon the facial skin if beclomethasone is delivered by face mask, and the manufacturers do recommend that a mouth piece be used. In our experience, however, young children tolerate face masks much more readily than mouthpieces, and this might therefore constitute a greater risk in long term treatment.

Clearly, if beclomethasone dipropionate suspension is to continue to be recommended on the basis of the undoubted efficacy of the drug itself then further clinical trials of its usefulness in the currently available dosage and in the appropriate age group are urgently required.

We thank the children and their parents. We also thank Professor D Hull, Dr P Barbor, Dr D Johnston, and Dr N Rutter for allowing us to study patients under their care. Financial support was gratefully received from the Asthma Research Council.

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Commentary

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The discrepancy between the similar studies of Storr *et al*[1] who obtained a positive result and Webb *et al* a negative one with the same drug, inhaled beclomethasone diproprionate, is puzzling and raises several questions.

The studies were similar but not identical insofar as Storr *et al's* was a double blind parallel study and Webb *et al's* a double blind crossover one, though this should not necessarily matter. Even so, there was a (non-significant) trend in favour of beclomethasone in that of Webb *et al* and the discrepancy may be in the study designs.

The most obvious difference is the dose inhaled, 2 ml (100 μg) versus 3 ml (150 μg), respectively. But the lower dose worked and the higher dose failed to do so, ruling out a dose related effect.

Nebulisation details were incomplete for both studies and in neither was the optimal liquid volume (usually drug+saline) of 4 ml used—this to reduce the proportion of dead volume left in the nebuliser after conclusion and to optimise the output.[2] It seems likely, however, that both systems produce similar respirable (about 2–5 μm) particles.[3] Nevertheless, the inescapable conclusion must be not that the drug does not work but that in the study of Webb *et al* it somehow failed to reach the lungs—such doses of beclomethasone have virtually no systemic effect.

In both studies the children inhaled the nebulised drug through a face mask, close fitting in the study of Storr *et al* and loose fitting in the study of Webb *et al*. With loose fitting masks much of the drug may impact on the face and lips, leaving little to be inhaled.[4]

Although it is difficult to pinpoint the error precisely, nevertheless, when using nebulised drugs, strict attention should be paid to the details of nebulisation and inhalation, otherwise anomalous results may arise.

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Archives of Disease in Childhood, 1986, **61,** 1111–1113

Inhalation powder and oral salbutamol combination

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SUMMARY Fifty six children with chronic asthma were treated with the inhaled dry powder of salbutamol or the combination of inhaled and oral salbutamol. Over three months the combination provided a significantly greater sustained symptomatic relief from asthma. Side effects were minimal and did not result in any withdrawals from the study.

We have previously shown the superior characterisics of combining tablets and inhaled dry powder of salbutamol in children with asthma on a short term basis. The combination had a rapid onset of effect and a sustained period of action. This initial study revealed no untoward side effects in the short term.[1]

To determine whether the combination treatment was superior to inhalation treatment alone in the symptomatic control of asthma over a three month period, we have performed a double blind placebo controlled trial. Specific attention was paid to the possibility of troublesome side effects during the study.

Patients and methods

Fifty eight children with moderately severe chronic asthma (grade C)[2] entered the study, and fifty six completed an assessment of three months. This group consisted of 38 boys and 18 girls. Their ages ranged from 4 to 12 years, with a mean age of 7·8 years.

A double blind placebo design was used, and the patients were assigned to one of two treatments by means of a randomisation code. The two groups did not differ significantly in terms of age range, sex difference, or duration and severity of asthma. The treatments were:

(1) Salbutamol 400 mcg capsules through a rotahaler given at 0800, 1400, and 2000h, and salbutamol tablets 4 mg taken after the inhalation.

(2) As treatment (1), except that the salbutamol tablets were replaced by identical looking placebo tablets containing lactose.

Both groups were permitted extra inhalational treatment in response to symptoms.

Before inclusion in the study each child's ability to inhale correctly from a rotahaler was confirmed.

For each of the three months that formed the study period a number of measures of the child's therapeutic response were obtained from a maternal daily diary record of symptoms. For each month the number of days on which each symptom was present—that is, symptom days—was recorded for the symptoms of night cough, night wheeze, day wheeze, day cough, and restriction of activity. A measure of the child's global response to treatment during each month was obtained by summing the number of symptom days for each of the above categories.

Additionally, the number of extra inhaled capsules, sympathomimetic nebuliser treatments, and admissions to hospital required were recorded throughout the three months. Recording of side effects and specific note of excitability or behavioural change was made. The children were reviewed monthly at an outpatient clinic where daily diary records were checked and any additional side effects recorded.

Results

Table 1 shows the relation between the mean symptom day scores over the three months and the treatment group to which the children had been assigned (powder and active tablet versus powder and placebo tablet). The results were analysed using two way analysis of variance in which the mean scores were contrasted over the two treatment groups (active; placebo) and the three months. The treatment factor was treated as a fixed factor and the time of measurement factor as a repeated measures factor. The results in Table 1 show the significant levels of the treatment factor only for each comparison. Table 1 shows that for all comparisons there was a tendency for the group of children treated with the active tablet to have fewer symptom days. This trend was significant for the measures of night cough, day cough, and total symptom scores. This suggests that treatment with the active tablet produced greater symptomatic relief of symptoms of asthma and particularly cough. This relief seemed to be sustained throughout the three months.

Table 2 compares the two groups for a number of measures of the need for additional treatment. These measures include the mean number of nebuliser treatments needed by the child during the three months, the mean number of additional capsules used by the child over and above the basic regimen of three each day, and the proportion of children who were admitted to hospital as a result of acute asthma. Table 2 suggests the presence of dramatic differences in the outcomes of the two treatments, with children receiving the active tablet requiring only 40% of the repeat nebulisations and half as many additional inhalations and having about 60% of the rate of admission to hospital when compared with the group assigned to placebo. Because of the fairly small numbers of subjects studied, however, these differences failed to reach significance, although the number of additional inhalations taken was of marginal significance ($p<0·1$).

Table 1 *Mean symptom days for subjects assigned to the active and placebo treatments*

Measure	*Treatment*	*Time of measurement (months)*			*p Value*
		1	*2*	*3*	
Night wheeze	Active	1·89	0·75	0·82	NS
	Placebo	2·19	1·78	1·41	
Night cough	Active	2·53	1·21	1·89	<0·05
	Placebo	4·52	2·89	2·85	
Day wheeze	Active	1·54	0·54	0·61	NS
	Placebo	1·52	1·37	0·81	
Day cough	Active	1·18	0·75	1·29	<0·05
	Placebo	2·15	2·04	2·26	
Restricted activity	Active	1·32	0·86	1·21	NS
	Placebo	0·93	1·70	1·30	
Total symptom days	Active	8·46	4·11	5·82	<0·05
	Placebo	11·31	9·78	8·63	

NS=Not significant.

Table 2 *Use of additional treatment during the three months in the active and placebo treatment groups*

Treatment	*Treatment group*		*p Value*
	Active	*Placebo*	
Mean No of nebulisers required	1·89	4·48	NS
Mean No of capsules taken on top of basic 3 each day	17·43	36·59	<0·1
% Admitted to hospital with acute asthma	28·6%	40·7%	NS

NS=Not significant.

Collectively, these findings provide a fairly convincing case for the view that the active tablet provided greater therapeutic benefit than the placebo tablet: children assigned to this regimen showed a consistent tendency to have fewer symptom days on all measures and were less prone to require additional treatment.

Of the original 58 children randomised to two groups, one child from each was eliminated because of failure to keep diary records. Of the remaining 56 children, there were eight reports of side effects, four from each group, although all continued on treatment and completed the three month evaluation.

In the active treatment group three children were regarded as being more active than usual, one for one month and two for all three months of the study. The other child was noted to have tremors for one week, but these abated spontaneously. In the placebo treatment group one child was regarded as overactive and had tremors, while two had headaches and the fourth was reported as lacking energy. These were regarded as minimal features and the children were continued on their regimen.

Discussion

This study has examined the extent to which giving paediatric patients with asthma treatment with salbutamol tablets in addition to inhalation powder provides greater sustained symptomatic relief from asthma. The results of the study clearly suggest that there are therapeutic benefits from this regimen as children receiving the active tablet had a consistent tendency to have fewer symptom days and required additional treatment less often. These findings are consistent with previous studies, which have shown that under controlled conditions over a short time the combination of powder and tablet provided a treatment with a time/response function that had a rapid onset (due largely to the rapid action of the powder component) and a sustained period of action (due largely to the longer acting effects of the tablet component). The present study shows that such effects do result in a reduction in both symptoms and the need for additional treatment when studied over a fairly prolonged period.

Few side effects were observed during the course of the trial, although it must be borne in mind that the number of subjects studied was fairly small. While overactivity was reported as the main problem in the combination group and headache in the group receiving inhalation only, none of the symptoms was severe enough to warrant stopping treatment nor did any family choose to do so unilaterally.

We conclude that this is a useful treatment for children able to inhale from a powder device and swallow tablets and may also provide a good alternative for those who are intolerant of theophyllines.[3]

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Fifty years ago

The blood-sugar in convulsions of infancy and childhood

Margaret B Maclean (Glasgow)—Arch Dis Child 1936;**11**:247–256

‘It has long been recognized that severe convulsive attacks are followed by depletion of the carbohydrate resources of the body.

‘Blood sugar estimations were made in a series of children admitted to hospital on account of convulsions, and an attempt was made to follow the changes occurring in the blood-sugar level from the beginning of a convulsion till some hours after it had ceased. The patients were aged from two days to eleven and a half years, and seizures were due to various causes. High blood sugar values occur most frequently in the first three hours after the convulsions, and hypoglycaemic readings were recorded most frequently between the fourth to twelfth hours. A blood sugar level of more than 180 mgm per cent was taken as indicating hyperglycaemia and one of less than 60 mgm per cent as hypoglycaemia.

‘Hyperglycaemia occurred most commonly in cases of tuberculous meningitis and hypoglycaemia after intracranial injury in the new born.

‘There are two possible explanations for the hypoglycaemia. It may be that violent muscular exertion uses all the available carbohydrate or that the central stimulation, acting as it does on the suprarenals, leads to exhaustion of adrenaline and to a cessation of glycogenolysis. The first suggestion is unlikely as the hypoglycaemia persisted in spite of taking food. To prove the second, adrenaline was injected when the hypoglycaemic stage was reached and there was an immediate response in two children; showing that the tissues are able to form glucose when adrenaline is supplied.’

(This paper raises the possibility that ‘in some children hypoglycaemia plays no part in the causation of convulsions but that the upset in carbohydrate metabolism is the result of them’. If fits do persist, or the child remains drowsy for an unusually long time, it may be justifiable to consider that there may be a lack of adrenaline, and instigate investigations and treatment accordingly. NEIL GORDON.)

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Serum antibodies to *Pseudomonas aeruginosa* in cystic fibrosis

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SUMMARY Serum IgG antibodies to *Pseudomonas aeruginosa* cell surface antigens were determined by enzyme linked immunosorbent assay. Titres in patients without cystic fibrosis were low (140–235). Those in patients with cystic fibrosis who were chronically infected by *P. aeruginosa* were very high (1100–20 500), while patients who grew the organism intermittently had lower titres (160–4400). Longitudinal studies showed that raised titres were observed at a very early stage of infection. High titres were associated with a poor clinical state, while low titres were associated with a better clinical state in both chronic and intermittently infected patients with cystic fibrosis. These results suggest that this test is a specific and sensitive measure of the severity and progress of the different stages of pulmonary infection by *P. aeruginosa* in patients with cystic fibrosis.

One of the most common causes of morbidity and subsequent mortality in cystic fibrosis is pulmonary infection, particularly by *Pseudomonas aeruginosa.*[1] Once *P. aeruginosa* is established in the lungs it is extremely difficult to eradicate, despite repeated courses of chemotherapy.

At present, there is no specific measure of the severity and progress of the early stages of *P. aeruginosa* infection. Growth of *P. aeruginosa* from the respiratory tract may be due to harmless colonisation or to an active infection.

The purpose of this study was to measure immunological changes associated with colonisation and infection of the respiratory tract by *P. aeruginosa* and to assess the value of these measurements in monitoring the progress of pulmonary infection.

Patients and methods

Patients. Serum samples, surplus to requirements, were obtained from 75 patients with cystic fibrosis who attended the paediatric and adult cystic fibrosis clinics at our hospital during a study period of 12 months. Diagnosis of the disease was confirmed by at least one sweat test.[2] The patients were divided into three groups. Group 1 comprised 31 patients with cystic fibrosis (20 girls and 11 boys), who had an age range of 1–17 years, with a mean (SE) of 15·4 (7·3) years. *P. aeruginosa* had never been isolated from their sputum. Group 2 comprised 22 patients with cystic fibrosis (12 girls and 10 boys), who had an age range of 4–25 years, with a mean (SE) of 11·8 (1·5) years. *P. aeruginosa* had been isolated from their sputum at least once, but they had no recognisable illness due to that organism. Group 3 comprised 22 patients with cystic fibrosis (11 girls and 11 boys), who had an age range of 6–23 years, with a mean (SE) of 15·7 (4·6) years. *P. aeruginosa* had been isolated continuously from their sputum for at least a year, and they had recognisable chest illness due to that organism. Two serum samples at least 12 months apart were available from five patients in group 2 and seven patients in group 3.

Overall clinical state was assessed by the Shwachman score.[3] A maximum of 25 points was awarded for each of the following: chest *x* ray film, nutrition, general activity, and physical examination. Declining scores indicated a worsening condition. Chest *x* ray films were assessed by the Chrispin-Norman score.[4] The possible scores were 0–38, with increasing score indicating increasing abnormality. Complete clinical evaluation within three days after the serum sample had been obtained, and repeated bacteriological results, were available for 16 patients. Serial serum samples were available for nine of these patients. All these patients are reported on.

Controls

The control group consisted of 17 patients (seven girls and 10 boys) who were attending the paediatric clinic at this hospital and from whom blood specimens were taken surplus to requirements. The mean (SE) age was 9·54 (1·42) years, ranging from 5 months to 15 years. None had any evidence of lung disease or *P. aeruginosa* infection. There were three cases of diabetes, two each of anaemia, short stature, severe retardation, and haematemesis, and one each of lethargy, intestinal polyp, oesophageal reflux, malaria, congenital emphysema, and hypothyroidism.

Serum. All samples were stored at −20°C until immediately before use.

Enzyme linked immunosorbent assay (ELISA). IgG antibodies to *P. aeruginosa* cell surface antigens were measured by ELISA. Seven strains of *P. aeruginosa* with serotypes 1, 3, 6, 9, 10, 11, and a strain that could not be serotyped were used.[5] These are the most commonly isolated serotypes in our unit. Washed cells were bound to microtitre plates (Immulon Grade A, Dynatech) then fixed by 0·5% vol/vol glutaraldehyde in phosphate buffered saline. Unbound sites were blocked by 1% vol/vol bovine serum albumin in phosphate buffered saline. A single serotype was used in each plate.

A pool of serum with high titres, diluted between 1:1500 and 1:50 000 in 1% bovine serum albumin in phosphate buffered saline, was used for a standard curve on each plate. One hundred microlitres of each standard and test serum was added and incubated in triplicate for 75 minutes at room temperature. After washing, 100 µl goat antihuman IgG (γ chain specific) conjugated to horseradish peroxidase (Zymed Laboratories, San Francisco) diluted 1:2000 was added and then incubated for two hours at room temperature. After washing, 100 µl enzyme substrate solution, containing 5 mg orthophenyldiamine and 20 µl of 12% vol/vol hydrogen peroxide in 10 ml citrate phosphate buffer, was added. After two minutes the reaction was stopped by the addition of 100 µl 4M sulphuric acid. Absorption at 492 nm was measured in a Titerteck plate reader. Absorbance was ≤0·10 in wells not containing any one of the following alone: adsorbed antigen; test serum; or labelled antibody.

The blank absorbance was subtracted from the test absorbance. This value was converted to a dilution by reference to the standard curve. The reciprocal of the dilution used for the patient's serum (1000 or 10 000) was divided by the reciprocal of the dilution obtained from the standard curve, multiplied by 1000 and expressed as a titre. Each serum sample was tested against all seven antigens on the same day. The titre presented here is the sum of these seven values.

Statistical analysis. The Student's *t* test, regression analysis to estimate the best fit, and Kendall's rank correlation test were used. Significance levels were for two tailed tests.[6]

Results

The serum IgG antibody titre against *P. aeruginosa* from the 17 control patients is shown in Figure 1. Titres ranged from 140–250. The mean (SE) was 200 (5·6). The upper limit (99·9% confidence limits) was 270. There was no correlation between titre and either age or sex.

In each of the three groups of patients there was a wide spread of IgG titres against *P. aeruginosa* (Fig. 1). The highest titres were in patients who grew *P. aeruginosa* continuously (group 3). Patients from whom this organism had been isolated intermittently (group 2) generally had lower titres, although there was some overlap between the two groups. There was a significant difference between the titres in these two groups ($p<0·002$). Titres of patients in group 1 (*P. aeruginosa* never isolated from sputum) varied between 140 and 805 and were significantly lower than group 2 ($p<0·1$) and group 3 ($p<0·001$). Titres of all three groups of patients with cystic fibrosis were significantly higher than the control group ($p<0·001$ for group 3, $p<0·05$ for group 2, and $p<0·1$ for group 1).

Titres from patients in group 2 fell into three subgroups. Titres of most patients (14/22) were between 300 and 700. Four patients, however, had titres greater than 1000, which were within the range of patients in group 3. Three of these four patients were tested twice, with an interval of one year between samples. *P. aeruginosa* had been isolated on five previous monthly investigations from one of these patients and continuously for four months from another patient. These patients may be on the borderline between group 2 and group 3. Another patient had a poor record of attendance at clinic and had not been examined in the previous 12 months, while *P. aeruginosa* had been isolated intermittently for nearly five years from the fourth patient. At the other extreme, there were four patients also in group 2 who had titres of not more than 200, well within the control range. All these serum samples

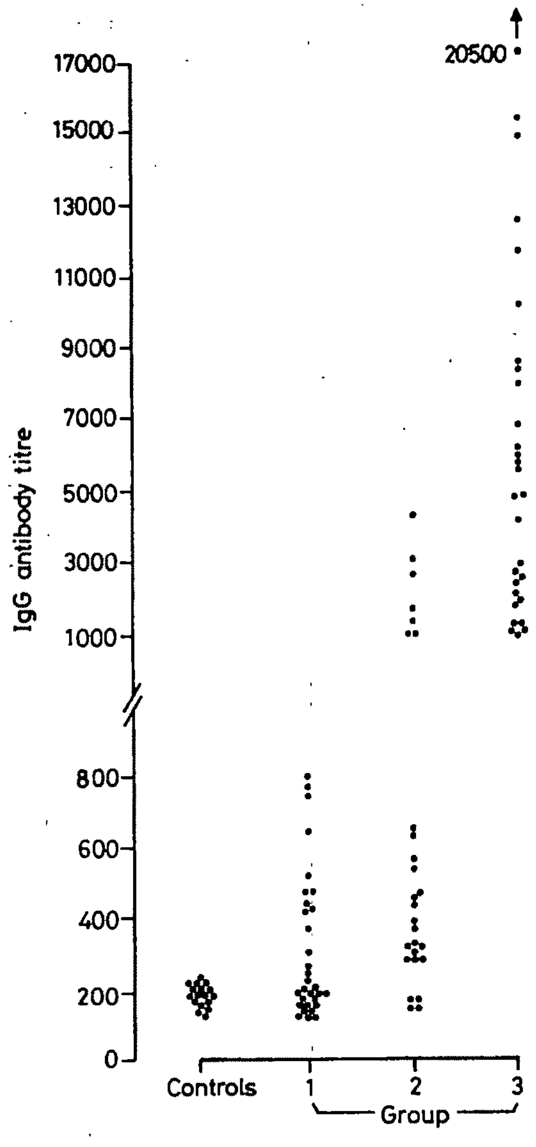

Fig. 1 *Serum IgG antibody titre to* P. aeruginosa *in patients with and without cystic fibrosis. IgG antibody titre is to* P. aeruginosa *serotypes 1, 3, 6, 9, 10, 11 and a strain that could not be serotyped.*

Controls: paediatric patients with no history of P. aeruginosa *infection; group 1: patients with cystic fibrosis from whom* P. aeruginosa *had never been isolated; group 2: patients with cystic fibrosis from whom* P. aeruginosa *had been isolated at least once; group 3: patients with cystic fibrosis from whom* P. aeruginosa *had been isolated continuously for at least one year.*

were obtained eight to 12 months after a single isolation of *P. aeruginosa* from sputum.

Titres from patients in group 1 fell into two subgroups. Nineteen had titres less than 300, which were within the normal range, and 12 had titres greater than 300, which were greater than the normal range.

These results showed that there was considerable variation in the titre of IgG antibodies to *P. aeruginosa* surface antigens among patients with cystic fibrosis. High titres were associated with patients in group 3. There was some overlap between titres found in patients in group 3 (chronic *P. aeruginosa* isolation) and patients in group 2 (intermittent *P. aeruginosa* isolation). Conversely, there were four patients in group 2 who had titres within the normal range.

Having established that there were differences in IgG titre to *P. aeruginosa* surface antigens among patients with cystic fibrosis, we evaluated the clinical importance of these findings. Clinical data, obtained within three days of the serum collection, was available for seven patients in group 2 and nine patients in group 3. It was thought that patients in group 1 deserved a separate study and are reported on elsewhere. The relation between IgG titre and Shwachman score is shown in Figure 2 and between IgG titre and Chrispin-Norman chest *x* ray score in Figure 3. There was a strong correlation between increasing IgG titre and deteriorating clinical state as measured by the Shwachman score ($\tau=-0{\cdot}6385$, $p<0{\cdot}01$). There was also a correlation between IgG titre and lung damage as measured by Chrispin-Norman *x* ray score ($\tau=+0{\cdot}4417$, $p<0{\cdot}10$).

Two or more serum samples were available from seven patients in group 3. They all behaved in a similar manner. Representative results of longitudinal studies for two patients in group 3 are shown in Figure 4. The IgG titre increased in all patients we investigated, even in those given repeated courses of intravenous treatment with antibiotics. The rate of

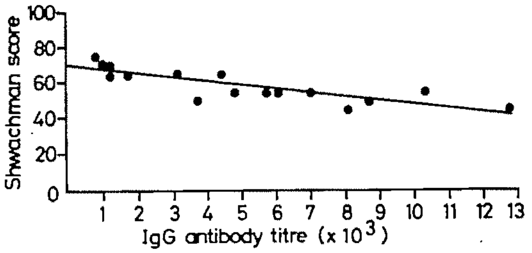

Fig. 2 *Relation between Shwachman score and serum IgG antibody titre to* P. aeruginosa *in patients with cystic fibrosis.*

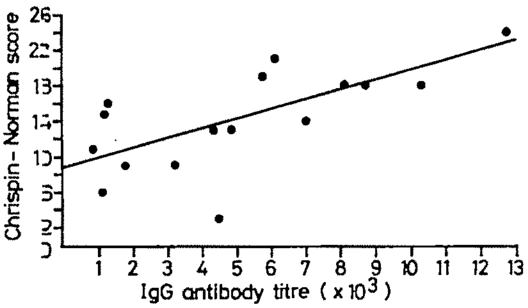

Fig. 3 *Relation between Chrispin-Norman score and serum IgG antibody titre in patients with cystic fibrosis.*

increase in titre varied in different patients. A rapid increase in titre was accompanied by a rapid decline in Shwachman score. Conversely, a slow increase in titre was accompanied by a more stable clinical state.

Longitudinal studies in two patients who were on the borderline between groups 2 and 3 are shown in Figure 5. In one patient *P. aeruginosa* had been present continuously since the initial isolation from sputum. In the other, *P. aeruginosa* had been isolated intermittently for three years. Intravenous anti-pseudomonal treatment was followed by a decrease in titre, after a lag of six to 10 weeks, in both patients. Throughout the period of investigation, changes in titre were the opposite of changes in Shwachman score in these patients.

Discussion

The purpose of this study was to assess the value of the measurement, by ELISA, of IgG antibodies to *P. aeruginosa* in monitoring the progress of pulmonary infection by the organism in patients with cystic fibrosis. Serum was tested against seven strains of *P. aeruginosa* with serotypes 1, 3, 6, 9, 10, 11 and a strain that could not be serotyped.[5] These represented 85% of isolates obtained from our patients during the previous six months.

Antibodies reacting with *P. aeruginosa* were

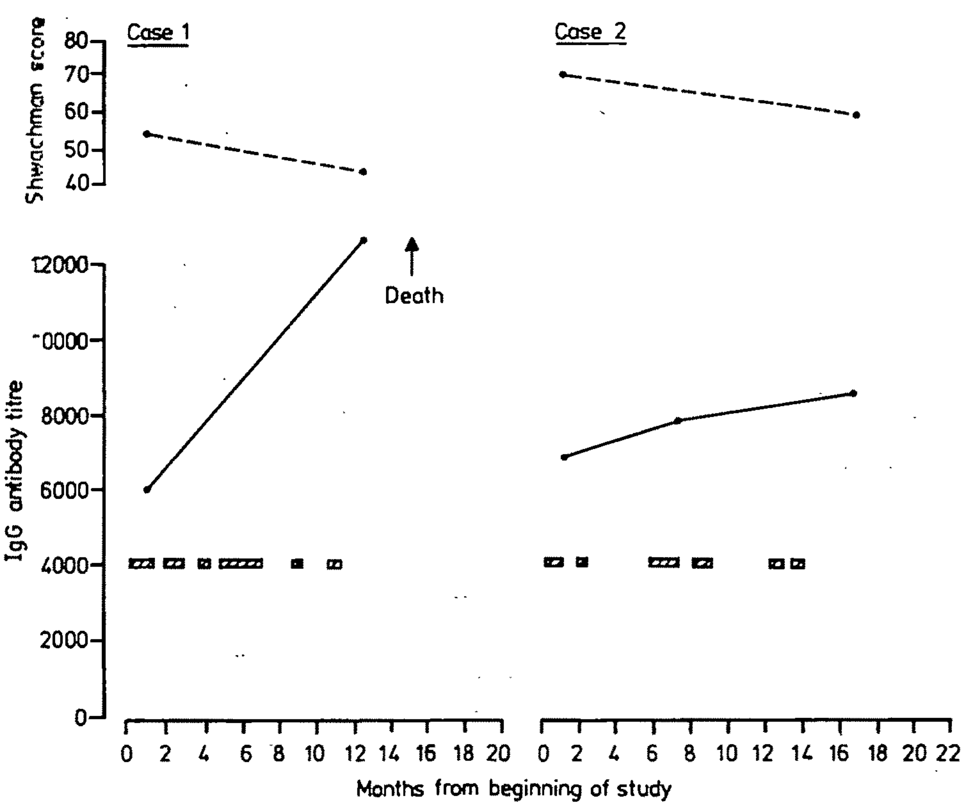

Fig. 4 *Longitudinal studies of serum IgG antibody titre and Shwachman score in two patients with cystic fibrosis chronically infected by* P. aeruginosa *(group 3). Hatched areas represent intravenous treatment with antibiotics.*

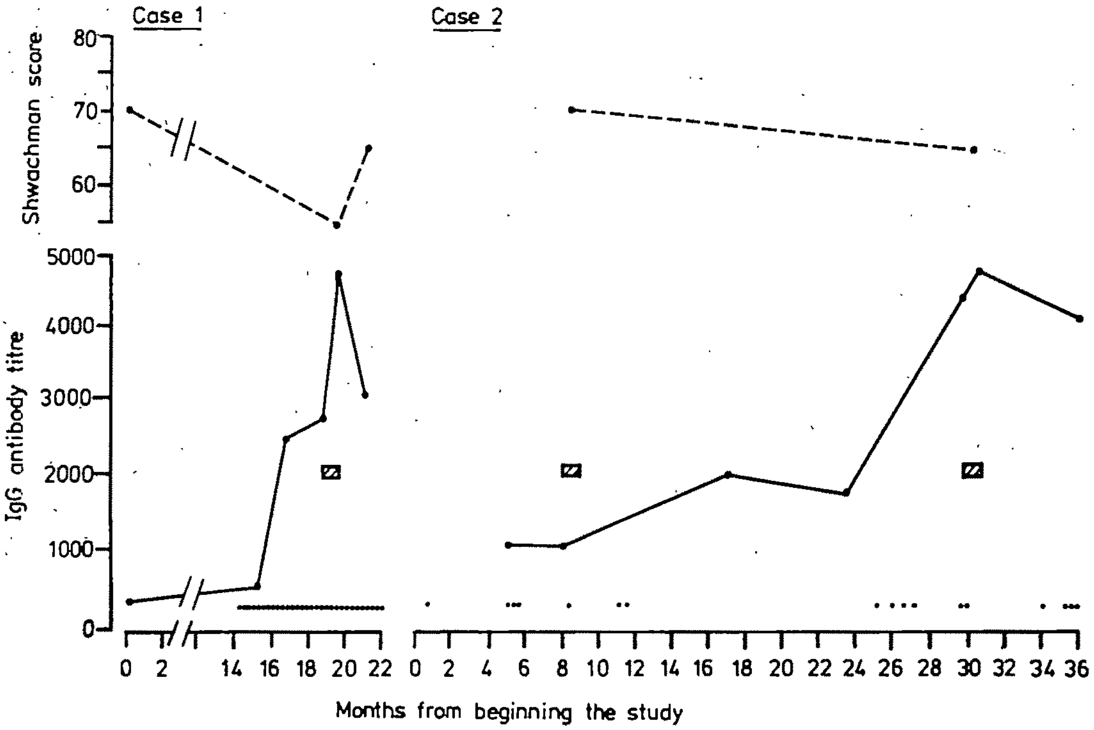

Fig. 5 *Longitudinal studies of serum IgG antibody titre and Shwachman score in two patients with cystic fibrosis in group 2. Hatched areas represent intravenous treatment with antibiotics. Dots denote* P. aeruginosa *isolated from sputum.*

present at low concentrations in patients without cystic fibrosis with no known *P. aeruginosa* infection. The mean titre was 200 and the upper limit (99·9% confidence limits) was 270. Hoiby, using counterimmunoelectrophoresis, has shown that the prevalence of precipitating antibodies against sonicated *P. aeruginosa* increased gradually with age in a normal population. These antibodies were present only at low titres, however, and were directed against two antigens that crossreacted with antigens from other bacterial species.[7] [8] In a survey of 100 adults of unspecified age, using ELISA, serum antibodies against *P. aeruginosa* surface antigens were also present at low concentrations.[9] One of our previous studies showed that crossreacting antibodies primarily directed against other Gram negative organisms did not make a significant contribution to the titre against *P. aeruginosa* in this assay.[10] Any titre greater than 300 was therefore considered greater than normal and indicative of the presence of a specific humoral response to *P. aeruginosa.*

Patients with cystic fibrosis who grew *P. aeruginosa* continuously had very high IgG titres, while patients who grew the organism intermittently generally had lower titres. There was some overlap, however, between the two groups of patients. This presumably reflects the arbitary division between the two groups. In contrast, other patients who grew *P. aeruginosa* intermittently had IgG titres within the range of normal values several months after a single isolation of *P. aeruginosa* from their sputum. The absence of a systemic humoral response may be due to the presence of *P. aeruginosa* in sputum that was transient or non-pathogenic. Alternatively, the absence of a systemic humoral response may be due to an early and adequate host response utilising secretory IgA antibodies or to an inadequate systemic immune response to the infection. It is unlikely that antibodies to *P. aeruginosa* were present in these patients' serum but not detected by this test. The serotypes of *P. aeruginosa* isolates from all these patients were among those included in the assay. In addition, the outer membrane proteins of *P. aeruginosa* are highly conserved.[11] [12] As used in this test they are likely to be accessible to antibodies present in the serum and should give a positive result. The possibility of an inadequate systemic immune response is unlikely. The serum IgG concentrations in these patients were 10·1 g/l, 13·1 g/l, 13·7 g/l, and 13·8 g/l, which are within the normal range (5–16 g/l) for their ages. Work is in progress to examine these possibilities.

High IgG titres were associated with poor clinical state, as measured by Shwachman score, and with evidence of lung damage, as measured by Chrispin-Norman *x* ray scores. Conversely, a low titre was associated with a good clinical state and *x* ray score. This was true for patients who grew *P. aeruginosa* continuously or intermittently.

These results confirm and extend those previously reported by Hoiby.[13–15] Using a sonicated preparation of *P. aeruginosa* cells and counterimmunoelectrophoresis, the number of precipitating antibodies increased with increasing duration of infection and correlated with a decrease in clinical state, but only in patients who had grown *P. aeruginosa* continuously for at least six months. The method used in this study showed an increase in IgG titres above control values at an earlier stage of infection. There are three possible reasons for this. First, ELISA is much more sensitive than counterimmunoelectrophoresis. Secondly, the antigen used was different. The antigen used in this work consisted of whole glutaraldehyde treated cells—that is, cell surface antigens that are in their native configuration. These are likely to be the major antigenic stimulus in the earliest stages of infection. Finally, only precipitating antibodies are detected by counterimmunoelectrophoresis, while both precipitating and non-precipitating antibodies are detected by ELISA.

Longitudinal studies revealed that the rate of increase in titre was fast or slow in different patients. The titres did not decrease in the seven patients studied who had grown *P. aeruginosa* for several years and who had high titres, even if they had received repeated courses of intravenous treatment with antibiotics. The continued antibody presence implies the continued presence of the appropriate antigen. These findings are in agreement with those of Doring and Hoiby.[16] A decrease in titres was observed, however, after intravenous treatment with antibiotics in patients who had grown *P. aeruginosa* for shorter periods. This decrease was apparent some weeks or months after treatment, in accordance with the normal delay in response by the humoral immune system.

Twelve of 31 patients with no known *P. aeruginosa* infection had titres greater than the normal range. Only one patient had an infection with any Gram negative organism. Antibodies directed against Gram negative organisms other than *P. aeruginosa* do not make a significant contribution to this assay.[10] It is extremely unlikely, therefore, that crossreacting antibodies were the cause of these raised titres but rather that they were indicative of a specific humoral response to *P. aeruginosa*. Most of these patients were fairly well and produced little or no sputum. Bacteriological findings were therefore based on throat swabs. Even in those patients who did produce sputum, organisms present in low numbers (less than 10^4 per ml) are unlikely to be detected by the protocol used in our laboratory. Longitudinal examination of the bacteriology and IgG titres of these patients is continuing.

The measurement of free serum IgG antibodies to *P. aeruginosa* by ELISA is now possible on a routine basis. It provides a specific, quantitative, and highly sensitive measure of immunological changes associated with all stages of pulmonary infection by *P. aeruginosa*. These changes correlate with changes in both the clinical state and the chest *x* ray film. The results presented here suggest that the ELISA may be a suitable test to differentiate between colonisation by *P. aeruginosa* (presence of the organism without appreciable tissue damage) and infection by *P. aeruginosa* (tissue invasion and damage). Longitudinal studies are in progress to provide further proof of this. Of particular importance is the ability to detect a systemic immune response to *P. aeruginosa*, and hence putative tissue invasion, before it is isolated from sputum. This may have far reaching implications on the treatment and prognosis of patients.

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Interaction between chloramphenicol and acetaminophen

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SUMMARY Acetaminophen has been reported either to prolong or not to affect the clearance of chloramphenicol. To confirm one of these findings we studied the clearance of chloramphenicol and its metabolites using high pressure liquid chromatography in five patients (ages 2·5 to 5 years) before and during oral treatment with acetaminophen (50 mg/kg/day). Significant differences were observed in mean (SD) peak serum chloramphenicol concentration (−9·7 (3·2) mg/l), mean (SD) apparent volume of distribution (+225 (162) ml/kg), mean (SD) chloramphenicol half life (−1·9 (1·1) hours), mean (SD) chloramphenicol clearance (+236 (94) ml/kg/h), mean (SD) area under the curve (−83·5 (33·0) mg/l/h), and mean (SD) elimination constant (+0·34 (0·13)h^{-1}) between samples obtained before and during treatment with acetaminophen. Acetaminophen, when given orally for several days, increased the clearance of chloramphenicol, perhaps by increased glucuronidation. This report re-emphasises the need for therapeutic drug monitoring whenever these two drugs are used together.

Haemophilus influenzae is the leading cause of bacterial sepsis and meningitis in children between the ages of 1 month and 5 years.[1] Chloramphenicol is a first line antibiotic for the treatment of invasive disease caused by ampicillin resistant *H. influenzae*.[2] Often these children have an increased temperature and are given antifever treatment. It has been reported that acetaminophen given intravenously prolongs the serum half life of chloramphenicol in adults.[3] Recently, Kearns *et al* observed no differences in the pharmacokinetics of chloramphenicol between patients who received acetaminophen orally and those who did not when these groups were compared after the first dose of chloramphenicol and from the seventh through the seventeenth doses.[4] Interestingly, they found that clearance of chloramphenicol significantly increased in those children who received acetaminophen between the steady state period and the final dose. The pharmacokinetics of chloramphenicol are extremely variable.[5] The inability of Kearns *et al* to detect differences between their two treatment groups may have been due to the design of their study. To clarify questions raised by these reports, we looked at the effect of oral acetaminophen on the clearance of chloramphenicol in subjects who served as their own controls.

Patients and methods

Five patients admitted to the Montreal Children's Hospital between December 1983 and November 1984 who had positive blood cultures for *H. influenzae* type b were studied. Their ages were 2·5, 2·5, 3·5, 4, and 5 years. Four subjects had epiglottitis and one had meningitis. None had received acetaminophen for the illness for which they were subsequently admitted to hospital. All subjects were initially treated with intravenous chloramphenicol 80 mg/kg/day and intravenous ampicillin 100–200 mg/kg/day until the culture results were known and the ampicillin was stopped. One patient received two doses of rifampin during the 48 hours before the first kinetic study was performed. After 48–72 hours of treatment with chloramphenicol a 24 hour urine collection was obtained for a chloramphenicol clearance. During this collection period, a heparin lock was placed and after a dose of chloramphenicol had been infused over 20 minutes 1 ml samples of blood were obtained 30 minutes and one, two, three, four, and six hours after the infusion was complete. The blood was allowed to clot, and the serum removed and stored at −70°C. At the completion of this 24 hour urine collection, oral acetaminophen 50 mg/kg/day every six hours was started. Each dose of acetaminophen was given 30 minutes before an infusion of chloramphenicol.

Forty eight to 72 hours after the start of treatment with acetaminophen urine was again collected over 24 hours for chloramphenicol clearance and the subject's blood was sampled at the time points noted above after an intravenous dose of chloramphenicol. Serum specimens for each subject were run together as a batch.

Acetaminophen, chloramphenicol, and chloramphenicol succinate concentrations in serum and urine samples and chloramphenicol glucuronide concentrations in urine samples were determined using a modified high pressure liquid chromotography technique described by Aravind *et al.*[6] In brief, 0·1 ml sodium acetate buffer pH 4·6 (1·0 N) and 1·0 ml ethyl acetate containing 20 μg/ml 5-ethyl-5-*p*-tolybarbituric acid (ETBA) were added to 0·05 ml spiked serum or patient's serum. After vortexing and centrifuging, the organic top layer was transferred to a clean tube and evaporated under air. The residue was resuspended in 0·05 ml methanol and 0·02 ml was injected into the column. Optimal resolution was achieved using a uBondapak C18 column with an eluent solution of methanol: water:acetic acid (37:62:1) over a period of 18 minutes with a flow rate of 1·5 ml/min at ambient temperature. Standard spiked solutions with ETBA as an internal standard were extracted according to the procedure outlined above. The average per cent recovery was 99%.

The drug concentrations were calculated by integration of the area under the curve of the chromatographic peak by the trapezoidal method. The average retention times for chloramphenicol, chloramphenicol succinate, glucuronide (from urine samples), and acetaminophen were 5·86, 8·5, 5·76, and 2·65 minutes, respectively. The coefficients of variance at 5, 15, and 25 mg/l of chloramphenicol were 5·8, 5·6, and 4·7%, respectively. Kinetic variables were analysed assuming a one compartment open model using areas under the time concentration curve (AUC) from 0 to infinity.

The serum concentrations of chloramphenicol and its metabolites were plotted semi-logarithmically. The elimination rate constant Kel and the serum half life ($t_{1/2}$) were computed from the slope of the drug disappearance curve. This slope was determined by the method of least squares; extrapolation to time zero generated the computed chloramphenicol concentration at time zero (Cp_O). The apparent volume of distribution (AVd) was calculated as dose/AUC/Kel. Chloramphenicol clearance (CC_L) was computed as dose/AUC. Chloramphenicol concentrations in serum and kinetic variables obtained before treatment with acetaminophen were compared with those obtained during treatment with acetaminophen using the *t* test for paired samples and Wilcoxon's matched pairs signed rank test.[7]

The protocol and consent form used in this study were approved by the Montreal Children's Hospital ethics committee. Consent was obtained from the parent and patient (if possible) before enrolment.

Results

Significant differences in Cp_O, AVd, $t_{1/2}$, CC_L, AUC, and Kel occurred between samples obtained before and during treatment with acetaminophen (Table 1). This change was greatest for CC_L, which

Table 1 *Chloramphenicol kinetic variables before and during treatment with acetaminophen for the five patients. Values are mean (SD)*

Kinetic variable	*Treatment with acetaminophen*		*p Value**
	Before	*During*	
CP_O (mg/l)	26·7 (5·7)	17·0 (4·9)	<0·003
AVd (ml/kg)	306 (78)	531 (202)	<0·04
Kel (h^{-1})	0·26 (0·09)	0·60 (0·15)	<0·004
$t_{1/2}$ (h)	3·0 (1·3)	1·2 (0·3)	=0·02
AUC (mg/l/h)	112·2 (42·6)	28·7 (12·2)	=0·005
CC_L (ml/kg/h)	78 (23)	314 (107)	<0·005

CP_O=Computed chloramphenicol concentration at time zero; AVd=apparent volume of distribution; Kel=elimination rate constant; $t_{1/2}$=serum half life; AUC=area under the time concentration curve from 0 to α; CC_L= chloramphenicol clearance.

**t* Test for paired samples, two tailed; p=0·04 for all variables by Wilcoxon's matched pairs signed rank test, two tailed.

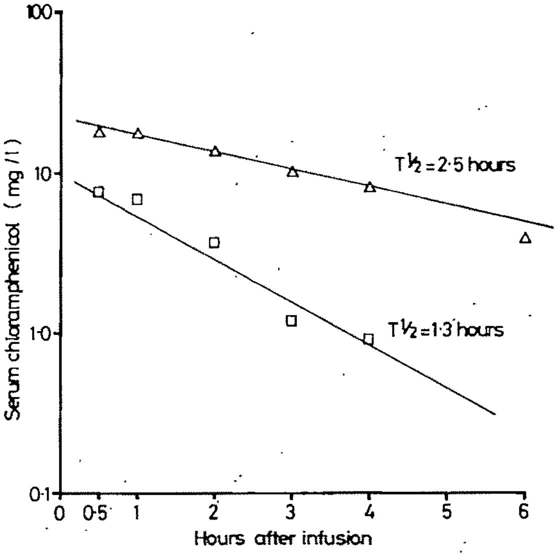

Figure *Chloramphenicol kinetics in the serum of a patient before (△) and during (□) treatment with acetaminophen.*

Table 2 *Urinary excretion of chloramphenicol and metabolites by the five patients before and during treatment with acetaminophen. Values are mean (SD) percentage of chloramphenicol (mg/l) excreted in the urine as chloramphenicol, chloramphenicol succinate, and chloramphenicol glucuronide*

Compound excreted	*Treatment with acetaminophen*	
	Before	*During*
Chloramphenicol	27·4 (5·9)	17·7 (6·2)*
Chloramphenicol succinate	69·1 (5·9)	72·2 (12·9)
Chloramphenicol glucuronide	3·5 (2·0)	10·1 (11·6)

*$p<0·05$ Compared with before treatment with acetaminophen, *t* test for paired samples, two tailed; $p=0·04$, Wilcoxin's matched pairs signed rank test, two tailed.

increased to a mean (SD) of 236 (94) ml/kg/h (a 303% increase from the level before treatment with acetaminophen). A representative serum disappearance curve in one patient is presented in the Figure. All patients recovered uneventfully, although one patient was unable to achieve a 30 minute peak chloramphenicol concentration in the 10–20 mg/l range considered therapeutic.

The percentage of chloramphenicol excreted in the urine as chloramphenicol, chloramphenicol succinate, and chloramphenicol glucuronide before and during treatment with acetaminophen is shown in Table 2.

Discussion

Our results, showing a decrease in CP_O, AUC, and $t_{1/2}$ and an increase in AVd, Kel, and CC_L during treatment with acetaminophen, contrast to those previously published. These differences may be explained by differences in assay techniques and study design. Buchanan and Moodley described six adult patients who were given 1 g of chloramphenicol intravenously, after which their serum chloramphenicol concentrations were monitored for two hours.[3] Acetaminophen 100 mg intravenously was then given and additional serum samples for chloramphenicol were taken over the next four hours. Serum chloramphenicol concentrations were determined using a microbiological assay. Urinary excretion of chloramphenicol metabolites was not determined.

Acetaminophen is rapidly absorbed from the gastrointestinal tract after oral administration; 10–32% of the drug is lost through first pass metabolism by the liver and does not reach the systemic circulation.[8] The drug is extensively metabolised, primarily by the liver. The major metabolite in adults is the glucuronide conjugate.[2] The use of intravenous acetaminophen in adults could result in higher peak blood concentrations and perhaps contribute to decreased chloramphenicol metabolism by competition for glucuronyl transferase activity. As sulphate conjugation of acetaminophen is the predominate route of degradation in children[9 10] a prolongation of the half life of chloramphenicol after a single intravenous infusion of acetaminophen may not be as pronounced.

The method used to determine chloramphenicol concentrations is another important difference between these studies. High pressure liquid chromatography is a highly sensitive and specific method. Buchanan and Moodley used a turbidimetric procedure, which measured inhibition of growth of *Shigella sonnei*.[11] The mean chloramphenicol concentration in their patients after treatment with acetaminophen was ≤10 mg/l. Microbiological methods, while measuring antimicrobial activity, are not specific for a particular drug. The patients in the earlier report had all received broad range antibiotics. What effect these other antibiotics may have had on the determination of chloramphenicol concentrations was not mentioned. A similar turbidimetric method had a sensitivity of 5–10 mg/l.[12] As the report by Buchanan and Moodley did not contain patients who received chloramphenicol alone we do not know whether the serum concentrations reported were a result of treatment with acetaminophen or whether their procedure did not allow for accurate determination of chloramphenicol concentrations at the time points after acetaminophen was given.

The report by Kearns and coworkers found no differences in chloramphenicol pharmacokinetics between 18 children who received acetaminophen and eight who did not during their admission to hospital;[4] 10 children treated with acetaminophen had received the drug before their admission. In addition, the selection process for those who received aspirin or no antifever drug was not clearly defined. Large differences exist in pharmacokinetic variables of chloramphenicol among normal subjects. The half life of chloramphenicol in paediatric patients has been reported to range between 1·7 and 12·0 hours.[5] To control for this extreme variability, it is important to use patients as their own controls whenever possible. The report by Kearns *et al* did find differences in pharmacokinetic variables between the first and last dose of chloramphenicol in those children who had not received acetaminophen before their admission to hospital and a significant increase in chloramphenicol clearance at the time of the last dose in those patients treated with acetaminophen.[4] The methodological problems with these earlier reports highlight the problems with pharmacokinetic studies when appropriate controls are not used.

One of our patients received two doses of rifampin within 48 hours of the first kinetic study. This patient's pharmacokinetic variables for chloramphenicol were similar to those of the other patients who did not receive acetaminophen. Treatment with rifampin has been reported to increase metabolism of itself and other drugs,[13-15] probably as a result of induction of drug metabolising enzymes as evidenced by a proliferation of smooth endoplasmic reticulum of the hepatocyte and increased glucuronidation.[16] Such activation is usually maximal 48 hours after induction. If treatment with rifampin affected our patient's metabolism of chloramphenicol the effect should have been present before the first kinetic study. The recent report of an effect of rifampin on chloramphenicol concentrations used peak serum concentrations, which can be affected by rate of drug infusion, and did not specify whether the patients received acetaminophen before admission to hospital.[17]

The accelerated chloramphenicol clearance after treatment with acetaminophen could not be attributed to state of hydration or fever as these clinical states were similar for both study periods. Moreover, the most substantial change was noted in the elimination rate constant (+131%), not AVd (+74%). This indicates that the increase in chloramphenicol clearance is due mainly to an accelerated elimination rate constant secondary to increased metabolism. This is supported by an almost twofold increase in the urinary excretion of the glucuronide metabolite (Table 2).

Age, rate of infusion, obesity, underlying disease, and other drugs that the patient is receiving have all been shown to effect the serum concentration of antibiotics administered intravenously. This report re-emphasises the need for therapeutic drug monitoring whenever drugs with narrow therapeutic index are used and the drug therapeutic concentrations are near the presumed toxic concentrations.

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Short reports

Sleep apnoea in infants with congenital stridor

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SUMMARY Indices of central apnoea, respiration rate, heart rate, and body movements were comparable in seven infants with congenital stridor (infantile larynx) and matched controls. Obstructive sleep apnoea was only observed in three of seven infants with stridor. Periodic breathing was less common in infants with stridor than in controls.

Guilleminault *et al* have reported death (attributed to sudden infant death syndrome) of an infant with congenital stridor in whom obstructive apnoea was shown during life.[1] As congenital stridor is not uncommon in infancy and as its severity is influenced by coincidental respiratory infection, we set out to study sleep apnoea in seven otherwise healthy infants with this condition.

Patients and methods

Seven infants with a history of stridor from birth or the early weeks of life were studied. There were four boys and three girls, with a mean gestation of 40 weeks (range 39–40 weeks) and mean birth weight of 3100 g (range 2670–4410 g), whose mean chronological and postconceptional ages were 10 weeks (range 7–15 weeks) and 50 weeks (range 47–55 weeks), respectively, when initial studies were conducted. In each case the diagnosis of congenital laryngeal stridor ('infantile larynx') was made on the basis of history, examination, and findings at laryngoscopy. Chest *x* ray films yielded normal results and visualisation of the tracheal air column and barium filled oesophagus by lateral *x* ray films of the neck excluded important tracheal or oesophageal compression. There was no clinical suspicion of cardiac or neurological abnormality. One infant had mild to moderate micrognathia. Apart from stridor these infants were otherwise well when studies were carried out.

Seven healthy normal infants, matched for sex, gestation, and postconceptional age (to within 2 weeks in six cases) were selected as controls. Four had had no previous illnesses, but three had suffered from respiratory infections from which they had recovered some weeks earlier. All were free of symptoms and apparently healthy when studied. Consent for participation in the study was obtained from parents of all infants after a detailed explanation of the purpose and plan of the proposed investigation.

Details of monitoring procedures and analytical methods are described in detail on pages 1057–8 in our accompanying paper.[2] Central apnoeic pauses were defined as periods during which there was absence of chest and abdominal movements and stopping of air flow at the nostrils for at least six seconds. Indices of central apnoea were assessed for apnoeic pauses >6 seconds in relation to sleep state. The mean duration of apnoeic pauses and the episode of apnoea of longest duration were noted. The frequency of occurrence and duration of periodic breathing and gross body movements were also computed.

Results

Table 1 gives the results for apnoea variables, per cent sleep, respiration rate, and heart rate in infants with stridor and matched controls. No differences were observed between corresponding variables. No infant had prolonged (>15 seconds) central apnoea. Recurrent brief (>3 and <6 seconds) episodes of obstructive apnoea was observed in three infants and prolonged (> 6 seconds) episodes of obstructive apnoea in one. No control infant had either prolonged episodes of central or episodes of obstructive apnoea.

Table 2 gives the results for gross body movements and periodic breathing. Number and duration of gross body movements were comparable in infants with stridor and their matched controls.

Table 1 *Apnoea variables, per cent sleep, and respiration and heart rates in relation to sleep phase in seven infants with stridor and their case controls. Values are mean (SE)*

	Sleep phase	*Index (n=7)*	*Control (n=7)*
Apnoea index	Active	0·44 (0·36)	0·29 (0·14)
	Quiet	0·36 (0·14)	0·38 (0·14)
Apnoea attack rate	Active	0·06 (0·05)	0·14 (0·02)
	Quiet	0·05 (0·02)	0·05 (0·02)
Episode of longest duration (sec)	Active	3·81 (1·87)	4·27 (1·55)
	Quiet	7·37 (1·57)	5·60 (1·52)
Mean duration of apnoea (sec)	Active	3·15 (1·49)	3·82 (1·36)
	Quiet	6·52 (1·15)	5·00 (1·32)
Apnoea per cent	Active	1·70 (1·36)	1·26 (0·57)
	Quiet	1·29 (0·50)	1·59 (0·56)
Sleep per cent	Active	39·10 (4·72)	43·40 (3·80)
	Quiet	48·40 (4·31)	44·30 (4·20)
Respiration rate	Active	37·00 (3·42)	39·00 (1·76)
	Quiet	31·40 (3·18)	34·60 (2·65)
Heart rate	Active	128·20 (4·41)	127·20 (2·63)
	Quiet	120·70 (3·98)	115·50 (5·70)

Mann-Whitney U statistical test applied but not significant for each variable.

Table 2 *Gross body movements and periodic breathing in relation to sleep phase in seven infants with stridor and their matched case controls. Values are mean (SE)*

	Sleep phase	*Infants with stridor at presentation*	*Matched control at presentation*
Body movements:			
Total duration (min/100 min sleep)	Active	3·55 (0·70)	6·95 (1·43)
	Quiet	1·71 (1·00)	1·23 (0·36)
No/100 min sleep	Active	23 (3·94)	29 (3·81)
	Quiet	18 (9·47)	10 (3·38)
Periodic breathing:			
Total duration (min/100 min sleep)	Active	0·73 (0·54)	2·18 (0·96)
	Quiet	0·30 (0·19)	0·61 (0·36)
No/100 min sleep	Active	2 (1·56)	5 (2·10)
	Quiet	1 (0·59)	1 (0·46)

Mann-Whitney U statistical test applied but not significant for each variable.

There was less periodic breathing in infants with stridor than in controls, but this difference did not reach significance.

Discussion

The results indicate that apnoea variables, per cent sleep, respiration rate, heart rate, and gross body movements were similar in infants with mild stridor and normal healthy controls in both active and quiet stages of sleep.

Brief or prolonged episodes of obstructive apnoea was occasionally observed in infants with stridor but not in matched controls. In their review of congenital stridor in infancy Kahn *et al* reported an infant in whom tracheomalacia had been diagnosed and who died suddenly and unexpectedly at 4–5 months of age.[3] In that condition stridor is predominantly expiratory and not inspiratory as in the present cases. Guilleminault *et al* reported the sudden death of a 5 month old infant who presented as a case of 'near miss' sudden infant death syndrome at 3 months of age.[1] Twenty four hour polygraphic sleep monitoring was carried out within 30 hours of her death. The data obtained were compared with those from healthy control infants and other infants with 'near miss' sudden infant death syndrome who were of similar age. The number of mixed and obstructive respiratory events was abnormally high in the case described. The finding of obstructive episodes of apnoea in three of the seven infants in the present series suggests that superimposed respiratory infection might increase still further the hazard of episodes of obstructive apnoea in such cases, with its attendant adverse effects on heart rate and oxygenation.

Periodic breathing, defined as two episodes of apnoea of 3 seconds or more within 20 seconds of each other,[4] was uncommon in infants with stridor, occurring in only two index cases and in each case control. This difference is obscured in the case control comparison (Table 2), which failed to show a significant reduction in periodic breathing in infants with stridor. It is conceivable that upper airways obstruction modifies feedback loops so as to influence central respiratory control mechanisms,[5] thereby reducing or abolishing periodic breathing. It is of interest that the case described above[1] had less periodic breathing than the controls selected.

We thank the parents who allowed us to study their infants and Mrs P Walker, who typed this manuscript. This study was supported by the Foundation for the Study of Infant Deaths (grant number 28/HS/78).

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Intestinal malabsorption in cystic fibrosis

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SUMMARY An oral solution containing lactulose and L-rhamnose was administered to six patients with cystic fibrosis. Intestinal absorption of both sugars was assessed by measurement of their urinary excretion. The lactulose: L-rhamnose excretion ratio was raised, supporting the hypothesis of an intestinal component to the malabsorption of cystic fibrosis.

While the role of pancreatic insufficiency in the pathogenesis of the malabsorption syndrome of cystic fibrosis has long been recognised, more recently an intestinal component to the malabsorption has been proposed.[1]

The small intestinal permeability to probe molecules is widely used in the study of small intestinal absorptive function. One such test showed that after oral ingestion of D-xylose patients with cystic fibrosis have higher blood concentrations of D-xylose than controls.[2] These results were not substantiated, however, by steady state perfusion experiments in isolated in vivo lengths of jejuna.[3] It was proposed that other mechanisms, such as altered gastrointestinal motility, decreased hepatic metabolism, or decreased renal excretion, might explain the raised blood D-xylose concentrations in cystic fibrosis.[3]

Another test compares the intestinal permeability to the monosaccharide L-rhamnose and the dissaccharide lactulose by simultaneously measuring their urinary excretion after oral ingestion of a solution containing both sugars.[4] The normal intestine is much less permeable to lactulose than to L-rhamnose, so that the lactulose:L-rhamnose excretion ratio (with both quantities expressed as a percentage of the oral dose ingested) is approximately 0·05.[4] In children the upper limit of normal is considered to be 0·07.[5] By studying alterations in the absorption of one substance relative to another, errors due to altered gastrointestinal motility, distribution after absorption, and renal excretion should be minimised.[4] In this study the lactulose-L-rhamnose test was performed in six patients with cystic fibrosis.

Patients and methods

Six patients (four boys and two girls) with a mean age of 12 years (range 8–15 years) participated in the study. All had the typical history of cystic fibrosis and raised concentrations of sweat electrolytes at the time of diagnosis. All patients were taking pancreatic enzyme substitutes.

After an overnight fast each patient ingested an oral load (80 ml) containing lactulose (5·3 g in 7·5 ml of 'Duphalac' syrup) and rhamnose (0·75 g). All urine passed over the next five hours was collected, its volume recorded, and a sample, preserved with merthiolate, frozen and stored for analysis.

Urine samples were analysed for lactulose and L-rhamnose by quantitative thin layer chromatography with five upward developments on silica gel layers (Schleicher and Schull F1500), with methanol/butanol 1-ol/water, 30/30/30, vol/vol as the solvent for the first two developments, butanol 1-ol/ethanol/acetic acid/water, 60/30/10/10, vol/vol as the solvent for the third and fifth developments, and butanol 1-ol/ethyl acetate/pyridine/acetic acid/water, 5/70/15/10/10, vol/vol as the solvent for the fourth development, using raffinose and fucose as internal standards. The sugars were measured by dipping in 1·4% wt/vol 4 aminobenzoic acid in 3·5% vol/vol orthophosphoric acid in methanol and heating for 10 minutes at 120–130°C, measuring the resulting colour by densitometry.

Each patient's height (m) and weight (kg) was measured and body mass index (height/weight^2) calculated. Forced vital capacity, forced expiratory volume in one second, and the ratio between these measurements was also measured in each patient. For the purpose of comparison, forced vital capacity was calculated as a percentage of that expected for patient's height.[6]

Standard statistical methods were used in attempting to correlate the lactulose:L-rhamnose excretion ratios with the clinical variables.

Results

The six subjects excreted 13–111 mg (median value 26·8 mg) lactulose and 19–89 mg (median value 26·5 mg) L-rhamnose in the five hours. The lactulose:L-rhamnose ratio was derived from the five hour sugar excretions expressed as a percentage of the oral dose. In these subjects excretion ratios were

Table *Urinary lactulose and L-rhamnose excretion expressed as a percentage of the oral dose ingested and the lactulose:L-rhamnose excretion ratios*

Case No	*% Recovery*		*Lactulose: L-rhamnose excretion ratio*
	Lactulose	*L-rhamnose*	
1	2·11	11·98	0·176
2	0·36	3·66	0·098
3	0·57	2·48	0·23
4	0·45	4·31	0·10
5	0·57	3·42	0·167
6	0·26	3·28	0·079

0·079–0·23 (median value 0·13) (Table). All of these ratios exceed 'normal' values.[5]

There was no significant correlation between the level of the lactulose:L-rhamnose excretion ratio and body mass index (r=−0·0594), forced vital capacity, (r=−0·717), or forced expiratory volume in one second: forced vital capacity ratio (r=−0·217) in these patients.

Discussion

This study supports the hypothesis that there is an intestinal component to the malabsorption of cystic fibrosis. The mechanism of this intestinal dysfunction is yet to be elucidated. It seems unlikely that alterations in carrier mediated transport mechanisms are important, as mediated processes contribute little to the absorption of lactulose and L-rhamnose.[4] It has been proposed that the presence of abnormal mucus overlying the intestinal mucosa may alter transport kinetics.[3]

The clinical implications of this intestinal mucosal dysfunction in cystic fibrosis remain to be explored. In this small group of subjects the lactulose:L-rhamnose excretion ratio did not correlate with any of the simple clinical variables selected.

We thank the children and their physicians Dr Watson and Dr McMahon. We thank Ms E Drummond for typing the manuscript.

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Gastrografin in acute meconium ileus equivalent

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SUMMARY Twenty five (37%) patients with cystic fibrosis attending our clinic have experienced acute meconium ileus equivalent. In one year 37 of 40 episodes were treated with single dose oral Gastrografin with an 81% success rate, 75% being treated as outpatients. Patients found this treatment preferable to other recommended treatment.

Meconium ileus equivalent is an important complication of cystic fibrosis that reports have suggested occurs in 10–20% of patients.[1 2]

Treatment is primarily preventative, using N-acetylcysteine, laxatives, and, in some cases, adjustment of pancreatic enzyme supplements. Surgery during acute attacks carries a high mortality and morbidity from bleeding, poor wound healing, and postoperative chest infections[3] and should be avoided through effective medical treatment. N-Acetylcysteine given both by nasogastric tube and by enema three times daily[3] and Gastrografin enemas[4] have been used successfully but are unpleasant and require admission to hospital. There is little published information about oral Gastrografin in relief of acute meconium ileus equivalent.

Patients and methods

Sixty seven patients aged 9 months to 23 years (mean age 9·8 years) who were attending the cystic fibrosis clinic at our hospital were entered into the study. Those who had experienced meconium ileus equivalent were noted, and those who had had episodes during a recent 12 month period were compared in detail with those who have never had meconium ileus equivalent.

Meconium ileus equivalent was defined as: colicky abdominal pain with a mass in the right iliac fossa plus either constipation or typical *x* ray changes, or both.[4]

The two groups were compared for sex, meconium ileus at birth, type of pancreatic enzyme supplement, and chronic *Pseudomonas* chest infection, using Fisher's exact probability test, and for age, Schwachman score, number of admissions to hospital, quantity of pancreatic enzyme supplement, and stool frequency, using the Mann-Whitney U test.

Results

Twenty five patients (37%) had had meconium ileus equivalent at some time. Fourteen children suffered a total of 40 episodes during a one year period.

Characteristics of the children with meconium ileus equivalent during the study and of those who had never had meconium ileus equivalent (n=42) are shown in the Table.

Twelve patients had experienced recurrent meconium ileus equivalent and were treated prophylactically during the study year, 10 with regular oral N-acetylcysteine and eight with laxatives.

A single dose of oral Gastrografin was given at the onset of symptoms on 37 occasions in 11 children. Four children aged 3–8·5 years received 50 ml and seven aged 6·6–19·3 years received 100 ml. All were asked to drink at least four times that volume of water or fruit squash.

Vomiting of the Gastrografin soon after it was taken occurred three times. The children, however, did not continue to vomit, and Gastrografin was subsequently tolerated well when the dose was divided over several hours. There were no other complications.

Thirty episodes (81%) were treated with a single dose. A second dose 24 hours later was needed on six occasions. Treatment failed only once, in an 11 year old girl who subsequently responded to a Gastrografin enema.

Twenty eight episodes (75%) were treated on an outpatient basis. Nine episodes were treated in hospital, but in only six (16%) was admission primarily for treatment of meconium ileus equivalent.

Discussion

Meconium ileus equivalent is a troublesome and potentially fatal complication of cystic fibrosis, the aetiology of which remains obscure.[1] We have found it to be more common than has previously been reported and to occur most often in older children who have more severe manifestations of cystic fibrosis and who are admitted to hospital often. Our

Table *Comparison of characteristics of children with meconium ileus equivalent and those who had never had meconium ileus equivalent during a 12 month period*

	Group		*p Value*
	With meconium ileus equivalent	*Without meconium ileus equivalent*	
No	14	42	NS
Sex (F:M)	11:3	20:22	NS
Age (yrs) (mean (range))	11·7 (3·1–19·3)	6·6 (0·7–23)	<0·01
Admissions/year (mean (range))	1·86 (0–5)	0·78 (0–5)	<0·05
Admissions/year, excluding those treated for meconium ileus equivalent (mean (range))	1·35 (0–5)		NS
Meconium ileus at birth (No (%))	4 (28)	4 (9)	NS
Mean Schwachman score	74	85	<0·05
Chronic *Pseudomonas* chest infections (%)	6 (42)	6 (14)	NS
Mean No of stools/day	2	1·98	NS
Type of enzyme (No (%)):			
Pancrease	10 (71)	24 (57)	NS
Other	4 (29)	18 (43)	NS
Enzyme/meal* (Pancrease equivalent)	2·6	2·5	NS

NS=Not significant.

*1 Pancrease=2 Cotazyme/Nutrizym or 3 Pancrex *v* Forte.

patients who had had meconium ileus equivalent did not have less well controlled steatorrhoea than those who had not had meconium ileus equivalent, and neither prophylactic treatment nor newer pancreatic enzyme supplements has reduced the incidence of meconium ileus equivalent.

The failure of prophylaxis necessitates adequate treatment to relieve attacks. Surgery is hazardous and should be avoided wherever possible.[3] Currently described regimens of medical management[3] [4] are effective but unpleasant and require admission to hospital.

Gastrografin is a radiological contrast medium, containing sodium diatrizoate 100 mg/ml, meglumine diatrizoate 660 mg/ml, and iodine 370 mg/ml, plus flavouring and wetting agents. It is hypertonic with an osmolality of 2150 MOsm/kg H_2O at 37°C. Absorption from the intestine is minimal.

When Gastrografin is given by enema to relieve obstruction in the newborn, or in older patients with cystic fibrosis with meconium ileus equivalent, the manufacturers recommend that it be diluted fourfold with water. In our hospital children who require Gastrografin enemas to relieve meconium ileus equivalent have been given 100–200 ml Gastrografin in three times that volume of water, under fluoroscopic control.

We have found smaller oral doses, 50 ml in children under 8 years and 100 ml in those 8 years and older, to be effective. All children drink at least four times that volume of water or fruit squash with the Gastrografin. None of our patients has developed dehydration after these doses of Gastrografin, and electrolytes measured in inpatients were normal.

Oral Gastrografin is contraindicated where there is pre-existing dehydration, prolonged obstruction, or evidence of acute abdomen or iodine sensitivity but may otherwise safely be given to children aged over 5 years as outpatients.

Oral Gastrografin is a simple, safe, and effective outpatient treatment. We consider it to be the treatment of choice in acute meconium ileus equivalent in cystic fibrosis.

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Spontaneous subhyaloid and retinal haemorrhages in an infant

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SUMMARY A 6 week old girl from a socially isolated family presented with seizures and was found to have a full fontanelle, retinal and subhyaloid haemorrhages, and anaemia. These findings were not the result of a shaking injury but of a ruptured intracerebral arterial aneurysm.

With vigilance for child abuse and awareness of the possibility of cerebral injury from shaking increasing, alternative explanations of the characteristic clinical features of shaking may be overlooked. We describe a child in whom the initial impression of abusive shaking was false.

Case report

The girl was born uneventfully at term weighing 3300 g, the first child to unmarried white parents living in poor circumstances. Her mother was aged 16 and her father 21 and unemployed. On the day of the child's admission at the age of 6 weeks, her father thought she was well when he fed her at 0600h. Four hours later her mother noticed a one minute episode of twitching of the left arm and hand. Similar episodes occurred at each feed of the day, but she sucked well and seemed normal between them. She screamed uncontrollably during her evening bath, with a further left sided seizure. At 2300h she awoke screaming and looked pale and sweaty. Her father telephoned the family doctor and returned to bed but later accompanied her to hospital and said that he had recently bounced the baby, sleeping in her pram, down the few steps to the garden.

Shortly after admission she had several momentary episodes of left sided clonic seizures. She was afebrile but pale and irritable. The fontanelle was full. There were extensive bilateral retinal haemorrhages and a large right subhyaloid haemorrhage. There were no signs of direct injury or neglect, no cranial bruit, and normal femoral pulses. The head circumference was normal.

Her haemoglobin concentration was 8·5 g/dl. Other investigations with normal findings included white blood cell count and blood film, coagulation studies, platelets, and a full *x* ray skeletal survey. Lumbar puncture showed moderataly blood stained cerebrospinal fluid with a xanthochromic supernatant and no evidence of infection.

A diagnosis was made of intracranial haemorrhage, probably resulting from shaking injury. She was transferred to the intensive care unit where an urgent computed tomogram of the brain showed a large intracerebral haematoma (Fig. 1). This was considered to be incompatible with injury and to suggest spontaneous bleeding.

Her condition stabilised rapidly without further seizures. Transfemoral right common carotid angiography was performed 36 hours after admission. This showed an arterial aneurysm lying distally in an ascending frontal branch of the right middle cerebral artery. At craniotomy on the seventh hospital day the haematoma was evacuated and the aneurysm in its cavity removed. The only postoperative complication was a transient left sided weakness and at the age of 1 year she is clinically and developmentally normal.

Discussion

It is increasingly recognised that infants are particularly susceptible to cerebral injury by shaking.[1 2] This may be accompanied by other clinical or radiological evidence of trauma but is often more subtle and difficult to establish. Retinal and subhyaloid haemorrhages are considered to be highly suggestive, if not pathognomonic, of the condition in infancy.[1 2] We emphasise that they are not necessarily the hallmark of shaking and the presence of such haemorrhages should not become uncriti-

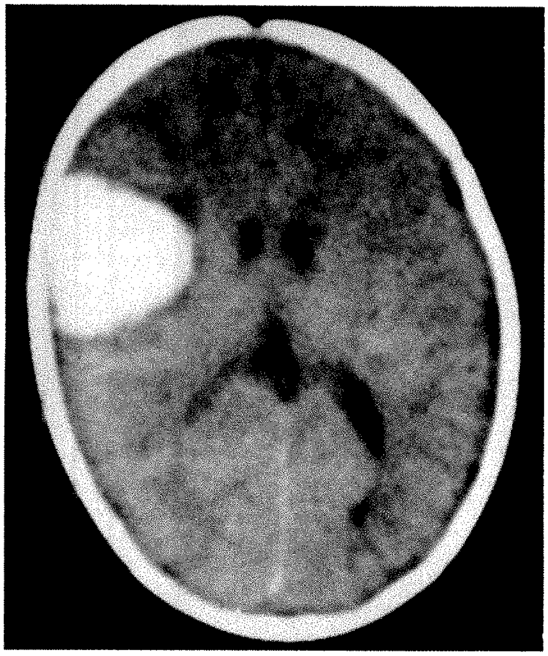

Fig. 1 *Computed tomogram of the brain of our case without contrast on admission showing a localised haematoma in the right frontoparietal area. (Compare with Fig. 2.)*

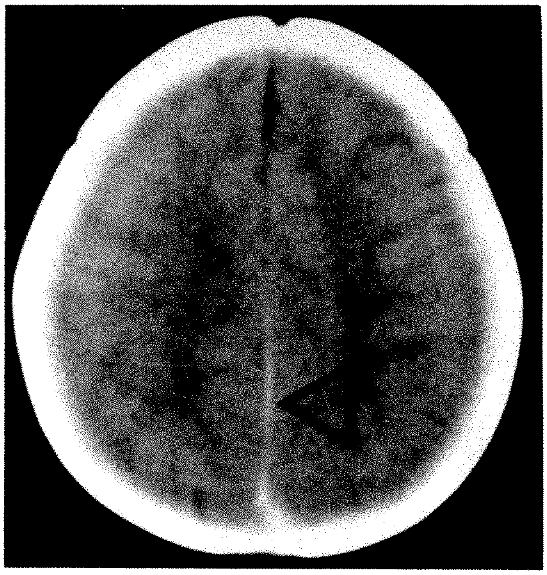

Fig. 2 *Computed tomogram of the brain without contrast in an 8 week old child with fatal shaking injury, showing a posterior interhemispheric subdural haemorrhage (arrow), which contrasts with the normal density of the falx anteriorly.*

cally incorporated into 'standard practice' as the sine qua non of abuse. Equal open mindedness to the interpretation of social factors in such cases should be maintained until a definite diagnosis has been made.

Like any other haemorrhage, those in the optic fundus may be traumatic or spontaneous. Among the spontaneous causes, a bleeding diathesis should be considered.[1] Diagnostic evaluation by computed tomography of the brain is also important. A localised intracerebral haematoma is most unlikely to be traumatic if there is no other evidence of parenchymal injury. Shaking may cause generalised brain contusion.[3] Alternatively, a subdural haemorrhage may be induced and a posterior interhemispheric distribution is particularly characteristic of shaking injury (Fig. 2).[4]

Recognition of a subdural haemorrhage by aspiration through the anterior fontanelle should also be considered critically. Any intracranial haemorrhage may leak into the subarachnoid space and a subdural haematoma can develop if an aneurysm or arteriovenous malformation ruptures through the arachnoid mater. Such a finding has been described in a 3 month old child with an intracerebral aneurysm.[5] Arteriovenous malformations may also occur within the meninges and so bleed directly into the subdural space. We can see little value in performing diagnostic subdural taps when access to computed tomography facilities are available.

We suggest that a computed tomogram of the brain should be considered urgently in the evaluation of cases of possible shaking injury or unexplained fundal haemorrhages. This should clarify the appropriate course to follow and prevent misinterpretation. A ruptured intracerebral arterial aneurysm may be eminently suitable for curative neurosurgery.[6]

We thank Dr Ian Holland for his neuroradiological expertise.

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Topical anaesthesia for venepuncture

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SUMMARY A topical anaesthetic cream was tested in a randomised, double blind, placebo controlled trial of 15 children. The severity of pain experienced during venepuncture was assessed, using visual analogue and verbal rating scales. The topical anaesthetic cream was found to be significantly superior to placebo using each form of assessment.

Venepuncture is probably the commonest procedure carried out on paediatric patients requiring medical treatment. Many children tolerate the procedure well, but for some it is a major ordeal. A topical preparation that could be applied without discomfort and alleviate the pain of venepuncture would be particularly useful for children receiving repeated venepunctures.

To penetrate intact skin a topical anaesthetic cream should contain local anaesthetic in high concentrations. This has hitherto been difficult to achieve because most anaesthetic bases are crystalline at room temperature and unstable in high concentrations. By mixing two anaesthetic bases, lignocaine and prilocaine, in equal proportions, an eutectic mixture is obtained that is liquid at room temperature. This mixture, known as EMLA (Eutectic Mixture of Local Anaesthetics), can be incorporated into an emulsion without first dissolving the bases in oil, making it possible to attain a higher concentration of active base for each emulsion droplet than has been previously achieved.[1] The water within the emulsion enhances skin penetration by the local anaesthetic.[2] On the basis of these properties, it can be predicted that the cream would afford good dermal analgesia.

The aim of the present study was to evaluate the analgesic effect of the anaesthetic cream with respect to venepuncture pain in children with leukaemia who were attending for repeated venepunctures.

Subjects and methods

Fifteen children receiving maintenance treatment for lymphoblastic leukaemia were asked to take part in the trial. Informed consent was obtained from patients and parents and the trial was approved by the local ethical committee.

The active preparation tested consisted of a mixture of lignocaine base 25 mg/ml and prilocaine base 25 mg/ml, together with an emulsifier (Arlatone) and a thickener (Carbopol). A placebo cream was prepared in which the active bases were substituted with Migyol 812 oil. This placebo was visually and cosmetically identical to the active cream. Both placebo and active cream were presented in identical 5g aluminium tubes.

Each patient was assigned a pack of four tubes. These were labelled 1–4 in order of administration and contained the treatment sequences A_1 P_2 A_3 P_4 or P_1 A_2 P_3 A_4 (A=active, P=placebo) as specified by a randomisation list. The trial was conducted double blind. The first application for each child was made in the clinic by the investigator, after which tubes 2–4 were taken home for the cream to be applied by a parent before subsequent clinic visits. The cream was always applied in a thick layer (roughly 2 ml each application) under an occlusive dressing, Tegaderm 3M, for a period of at least 60 minutes before performing the venepuncture. At the end of this time the dressing and cream were removed and the site cleansed with 0·5% chlorhexidine in 70% ethanol. Venepunctures were performed on the dorsum of the hand or the antecubital fossa, using a 21 or 23 gauge needle. A total of seven clinicians and nursing staff were involved in performing the venepunctures.

Venepuncture pain was assessed using a 100 mm visual analogue scale and a four category verbal rating scale. The response categories were: (1) no pain; (2) some pain but less than a normal venepuncture; (3) the same degree of pain as a normal venepuncture; and (4) more painful than a normal venepuncture. In most cases the assessment was made by the child. In the case of younger children the assessment was made with the aid of the parent.

'Ease of venepuncture' was assessed by the operator, using a three point verbal response scale, categorised as: (1) easier than usual; (2) the same as usual; and (3) more difficult than usual.

At the end of the trial the value of the active cream was assessed by asking the parents whether they found the cream useful and worth while.

Statistical analysis. Non-parametric statistical methods were used throughout. The data for all variables was analysed using Friedman's ANOVA. The multiple comparisons test based on Friedman rank sums and Fisher's exact test were used to examine treatment differences in greater detail.

Results

Fourteen children completed the study. There were eight boys and six girls aged 1–14 years, with a mean age of 7 years. One patient, a 4 year old girl, refused to have further applications of cream after her second visit because she disliked the occlusive dressing.

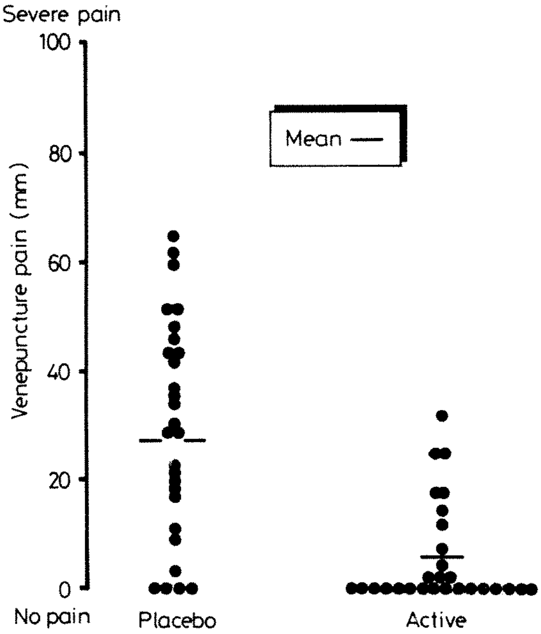

Figure. *Distribution of pain scores on the visual analogue scale as reported by children with leukaemia treated with active or placebo cream.*

$p<0{\cdot}0005$. Friedman non-parametric two way ANOVA.

The distribution of pain scores on the visual analogue scales is shown in the Figure. There was a highly significant difference between the values for the active cream and the placebo ($p<0\cdot0005$).

The results on the four point verbal response scale of venepuncture pain also showed that the active cream was significantly superior to placebo. (Fisher's exact test, $p<0\cdot01$) There was no difference between the two treatments with respect to ease of venepuncture.

Most parents and patients considered the use of the active cream worth while. Parents were able to apply the cream to a suitable vein at home without difficulty. There were several occasions when patients had to wait for the cream to take effect, but this inconvenience was considered to be offset by the advantage of less painful venepuncture. Eleven of the 15 children or their parents said they would like to continue using the active cream.

There were occasional skin reactions, consisting of pallor or redness, to both active cream and placebo. These were transient and clinically unimportant.

Discussion

The results of this study clearly indicate that an anaesthetic cream is an effective agent for alleviation of venepuncture pain. It is slightly inconvenient to use, but many children requiring regular venepuncture seem to be sufficiently motivated to accept this. Most children in this study elected to continue using the active cream for subsequent venepuncture.

The factors affecting absorption of local anaesthetic through intact skin have been studied by Evers, who found it necessary to use a thick layer of cream as emulsion droplets in contact with the skin readily became depleted of local anaesthetic.[3] In the same study percutaneous absorption of lignocaine and prilocaine into the systemic circulation was found to be measurable but slight.

As in all local anaesthetic preparations it is necessary to consider the potential for hypersensitive reactions. There is an extensive clinical experience with lignocaine and prilocaine given by injection, and true allergic reactions are extremely rare. There is no reason to believe that these agents applied topically will behave differently.

We acknowledge the help of Astra Pharmaceuticals Ltd.

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Meningitis due to *Haemophilus influenzae* resistant to ampicillin and chloramphenicol

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SUMMARY A case of ampicillin and chloramphenicol resistant *Haemophilus influenzae* meningitis successfully treated with cefotaxime is described.

Meningitis due to *Haemophilus influenzae* resistant to chloramphenicol and ampicillin is a recognised problem in the United States[1] but has only been reported once in the United Kingdom.[2] To our knowledge the case reported here is the first British case to be treated with cefotaxime.

Case report

A previously healthy 7 month old boy presented in

March 1986 with a one day history of lethargy, diarrhoea, and vomiting. On examination he was found to be febrile (38°C) with pronounced neck and spinal rigidity. Initial investigation revealed a leucocytosis of 25 000×10^6 cells/l (83% polymorphs) and blood glucose concentration of 4·5 mmol/l (81 mg/100 ml). Cerebrospinal fluid (CSF) findings were as follows: white blood cell count 4800×10^6/l (85% polymorphs and 15% lymphocytes), red blood cell count 240×10^6/l, protein: >1·0 g/l (100 mg/100 ml), glucose: <1·0 mmol/l. A Gram stain of the deposit showed pleomorphic Gram negative rods.

According to local practice treatment with chloramphenicol and penicillin was begun.

After overnight incubation *H. influenzae*, capsular type b, biotype 1, was isolated from CSF and blood. The organism was subsequently found to be resistant to chloramphenicol and ampicillin but sensitive to cefotaxime and co-trimoxazole by comparative disc diffusion methods, using a local wild strain of *H. influenzae* as the control. Resistance to ampicillin was confirmed by showing production of β-lactamase, using a plate incorporation acidometric method (minimal inhibitory concentration being greater than 64 mg/l).

The minimal inhibitory concentration to chloramphenicol was 16 mg/l, and production of acetyl transferase activity was shown by the rapid method of Slack *et al.*[3]

Treatment was changed to cefotaxime (150 mg/kg/day in two divided doses). Repeat lumbar puncture after six days revealed a reduction in white blood cell count to 760×10^6/l (56% polymorphs), a protein of 0·4 g/l, and a glucose of 2·1 mmol/l. CSF culture for bacteria yielded negative results. The CSF was bactericidal against the organism to a titre of 16. The child made a slow but complete recovery with 10 days' treatment.

Discussion

H. influenzae type b resistant to ampicillin and chloramphenicol was first reported in Bangkok in 1979 as the cause of an outbreak of meningitis.[4] A case of skin infection followed by respiratory infection reported in the UK in 1982 was subsequently found to be due to a non-capsule strain.[5] The first British report of a capsulate strain causing meningitis was successfully treated with latamoxef and co-trimoxazole.

Multiply resistant *H. influenzae* is currently increasing in prevalence in the USA to the extent that extended range (third generation) cephalosporins have been considered in the first line treatment of childhood meningitis.[6] Although the number of British reports is still small, any increase may force a similar review of our 'standard' treatment.

We thank the Public Health/Microbiology Laboratory at the John Radcliffe Hospital, Oxford, for their confirmation of the capsular typing and biotype of the isolate.

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Stool water in preterm neonates

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SUMMARY Data are presented on faecal water losses in 93 preterm infants being fed breast milk (72 infant days) or formula (280 days). Losses per kg increased to 4 weeks, when they amounted to 11% of water requirement in infants fed breast milk and 8% in infants fed formula.

There are no generally available data of faecal water loss in preterm infants. Losses in full term infants are said to be about 10 ml/kg daily,[1] or approximately 13% of total daily water requirement.[2] Values for small numbers of preterm infants have been published by Friis Hansen[3] and Senterre[4 5] and suggest a smaller loss of the order of 5–10 ml/kg daily, remaining fairly constant during the early weeks of life. This paper examines faecal water losses in a larger series of preterm infants at different weights and postnatal ages, and provides up to date information, previously unavailable, on stool water content in infants of very low weight.

Patients and methods

Faeces were collected during the course of energy and nitrogen balances at various postnatal ages in 93 preterm infants (24–35 weeks' gestation), weighing between 770 and 2085 g. Complete 24 hour collections were made on 352 days, of which 72 were during breast milk feedings and 280 during formula feedings. No infants were receiving intravenous feeding during the collections. At least two days of collection were made in each infant, and in some cases as many as 10. Faeces were collected between carmine markers, using rayon napkin liners (Boots). These liners are effective at preventing the transfer of water into or out of the stool, provided the stool is formed or semi-formed.[6] We have not presented data on completely unformed stools. Stools were frozen at −24°C in sealed plastic bags together with their liners, which were of known weight. Twenty four hour aggregates were weighed wet and were then reweighed after freeze drying. The difference in weight represented the water content.

Oral feed intake in most infants was between 180 and 200 ml/kg/day after the end of the first week.

Table *Stool water loss (ml/kg/day) at various postnatal ages* in breast milk and formula fed preterm infants of 24–35 weeks' gestation (mean (SD))*

Postnatal age (weeks)	*Preterm infants grouped according to feed*			
	Breast milk		*Formula*	
	Stool water loss	*n=*	*Stool water loss*	*n=*
1	15·7 (8·6)	15	8·6 (3·1)	18
2	16·3 (13·8)	15	11·2 (3·8)	25
3	19·6 (11·8)	14	11·1 (3·0)†	24
4	14·8 (12·6)	10	9·6 (2·6)	18
5 and 6	11·5 (9·0)	11	7·8 (4·9)†	21

*During each postnatal week the values for each individual infant were represented by the mean of at least two 24 hour stool collections.

†For formula fed infants at postnatal ages of 3 and 5 and 6 weeks, $t=2·72$ and $p<0·05$ for mean (SD) stool water loss.

Results

The Table shows the faecal water loss (ml/kg/day) at various postnatal ages in breast milk fed and formula fed infants. Losses were greater on breast milk feeds, but the difference was only significant during the first 14 days; thereafter the variability of stool water content in the breast fed infants was too large for significance to be achieved. Losses increased with postnatal age until the fourth week and then declined. There was no further change after the sixth week, though the variance continued to diminish. No significant correlation was found between stool water losses (ml/kg/day) and body weight ($r-0·23$, $p>0·05$) or gestation ($r-0·18$, $p>0·05$), but there was a highly significant correlation between total wet stool weight and daily stool water losses (Figure).

At an intake of 180 ml/kg/day, faecal water losses amounted to about 11% of the water requirement during the fourth week in breast milk fed infants and to about 8% in formula fed infants. In individual infants, however, as much as 24% of the intake could occur in the stool on occasions.

Discussion

Water balance is important for preterm infants because of high insensible losses and imperfect renal concentrating ability. Stool water losses, though rarely measured, may be an important factor in

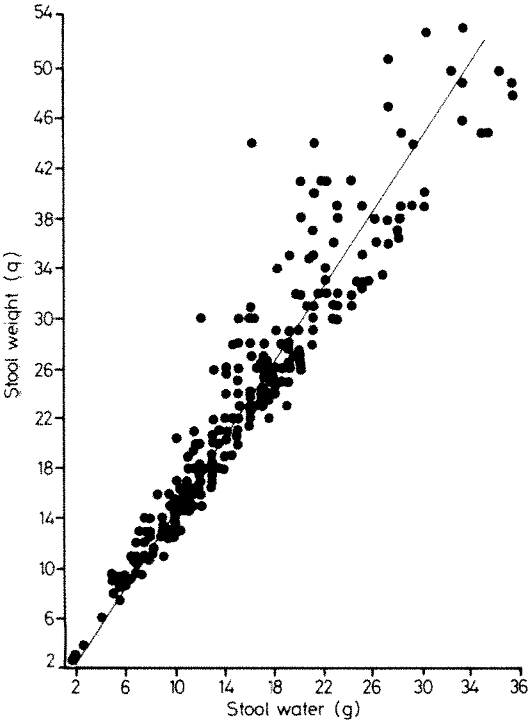

Figure *Relation between total wet stool weight and stool water loss.*

overall water economy and need to be taken into account in calculations of water balance. Our data provide information on stool water content from a large number of preterm infants and show that body weight and gestation are not important variables in determining stool water losses, but the type of feeding and the postnatal age do need to be taken into account. Water losses were 45% greater on breast milk than on formula and seem to increase during the first two weeks (presumably due to the increase in feed intake that occurs during this period), declining again to a stable level after the fourth week. Senterre found similar differences between breast fed and formula fed preterm infants (10 *v* 7 ml/kg/day) to those in our infants after the fifth week, but he did not examine postnatal age relations. Our results show that considerably greater allowances need to be made for younger infants fed breast milk.

It is not difficult to weigh stools at the bedside using preweighed liners and modern electronic balances. Stool water can be calculated from stool weight using the Figure, from which it can be seen that 10 g stool contains approximately 7 g water. The increasing scatter at high stool weights certainly reflects the greater fat content of such stools.

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Personal practice

Percutaneous insertion of central venous feeding catheters

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Since 1968 when Wilmore and Dudrick described normal growth and development in a child receiving all nutrients intravenously,[1] the practice of total parenteral nutrition in infants and children has become established as a life saving procedure.[2] Maintaining the infusion of hypertonic feeding solutions by the use of peripheral veins over anything but short periods is unpleasant for the patients and becomes increasingly technically difficult, especially in small babies. An alternative approach that employs central venous catheterisation is convenient for the patient but depends upon the availability of skilled surgeons and theatre facilities. In addition, it carries with it certain risks, particularly serious infection. In 1973 Shaw described a simple way of inserting central feeding lines percutaneously when administering total parenteral nutrition to sick low birthweight babies on special care baby units,[3] where it has since become an established practice.[4] The same technique has also been advocated for use in older children.[5] We have found this method well suited to small babies under 1 year of age recovering from gastrointestinal surgery or with other indications for total parenteral nutrition.

In our hospital all patients receiving total parenteral nutrition are initially referred to a nutritional care team for assessment and daily supervision of fluid and nutritional requirements. In addition, one member of this team (JP) has inserted a central venous feeding line if requested, using the technique described by Shaw.[3] The patient is thereby spared a surgical procedure and anaesthetic, while pressure of work on busy surgical colleagues and theatre staff is reduced. The whole process is less labour intensive than surgical insertion and therefore considerably cheaper.

Methods

The procedure is performed on the ward with the child left in his incubator or cot. As the technique is little different to siting a drip as far as the patient is concerned parental consent is not requested; sedation is unnecessary. The operator identifies a suitable vein: in the scalp one running in front of the ear is preferable and in the arm a median cubital vein. The long saphenous vein or one on the hand may also be used. The distance from the chosen vein to the right nipple is measured and this gives the approximate length to which the line must be inserted to place the tip within the right atrium.

A stainless steel trolley is laid up with a cut down set from theatre. The operator wears cap, mask, gown, and gloves. The latter should be powder free if possible or otherwise washed in sterile water to prevent powder contaminating the feeding line when handling. A sterile no touch technique is used throughout the following procedure; a nurse assistant is needed to hold the baby still.

The skin is cleaned with chlorhexidine 5% in 70% methylated spirit; sterile towels are used to drape the surrounding area. The Silastic feeding line (0·30 mm internal diameter, 0·64 mm external diameter)* is removed from the packet in which it has been autoclaved and cut to a length roughly 15 cm longer than that required for insertion into the vein. This is most conveniently measured using a sterile paper tape measure autoclaved together with the line. Next, a 5 ml syringe is filled with heparinised saline (5 units in 5 ml 0·9% saline) and attached to a 25G Butterfly needle,* the cutting edge of which is first blunted using the ridged surface of a needle holder from the cut down pack. The cylindrical plastic guard removed from the Butterfly is retained for later use.

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*Silastic feeding line (0·3 mm internal diameter, 0·64 mm external diameter) (Catalogue Number 602·105) is available from Dow Corning, ABCO House, Reading, Berks.

*19G and 25G Butterfly needles are available from Abbott Laboratories, Hospital Products Division, Queenborough, Kent ME11 5EL.

A 19G Butterfly needle* with the plastic tubing cut off is used to enter the vein. The assistant brings up the vein, if a limb is being used, by gentle squeezing around the proximal part. For a scalp vein finger pressure distally will distend the vein adequately. Blood flowing back through the needle can be controlled by light pressure over the needle tip. The Silastic feeding line is grasped with fine forceps and inserted into the needle and up the vein several millimetres at a time. If an arm vein is cannulated, the line may stick at the shoulder. This is more likely to happen the more lateral the vein, but abduction or other movement of the arm will often allow the line to be further advanced. Similarly, if the long saphenous vein is used progress may be obstructed at the groin; this can be overcome by manipulating the leg while pushing on the line. Insertion from a scalp vein may be interrupted as the line reaches the neck only to continue if the shoulders are rotated.

The line once inserted to the desired distance is held firmly in place by taping to the skin. The 19G Butterfly is now discarded and the retained plastic needle guard threaded over the end of the Silastic line. Once the 25G Butterfly is inserted for its full length into the line the guard can be slipped back into place on the needle and thus protect the Silastic from damage by movement against the bevel. The blunting of the needle reduces the risk of perforating the line while being inserted. The guard is held in position by sandwiching between two pieces of Elastoplast on the dorsal and ventral surfaces of the Butterfly, extending from just beyond the guard tip to the wings of the Butterfly (Figure). The line can now be flushed through with heparinised saline, and, if in a large blood vessel, gentle suction on the syringe will immediately cause the line to fill with blood. If blood cannot be aspirated the line is almost certainly in a small vessel unsuitable for hypertonic fluid administration. The position must always be checked radiographically using a 1 ml injection of Hypaque 25%. Ideally, the line tip should be sited just within the right atrium to allow maximum dilution of feeding fluids. If it has not been possible to advance beyond a peripheral vein the line may be used as a peripheral drip, but thrombophlebitis usually ensues within a few days.

The excess line is coiled up on the skin and covered with a small piece of sterile gauze held in place by Elastoplast tape. If insertion is from the scalp spraying the surrounding skin before applying the Elastoplast with Nobecutane Aerosol provides a sticky resin that will help hold the tape in place for weeks if necessary. For arm or leg insertions, circumferential Elastoplast strapping should be wound around the limb, starting distally until the whole butterfly and line assembly are covered together with the insertion site. We do not routinely disturb these dressings, but suspected sepsis at a later date would warrant inspection of the line entry site. Limbs should be splinted if the feeding catheter is running across a joint.

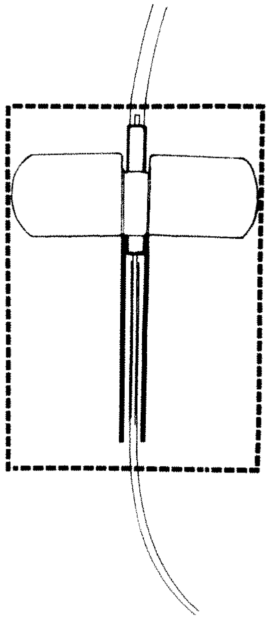

Figure *Diagram illustrating needle feeding line assembly, with position of elastoplast indicated by dotted line.*

Patients and results

From March 1984 to August 1985, 138 patients were referred to the nutritional care team for total parenteral nutrition, 37 together with the request that a percutaneous central venous feeding line be inserted. Twenty two patients weighed more than 3000 g and 15 less than 3000 g, with a range of 1000–7000 g.

In 31 patients catheter insertion to the right atrium was successfully accomplished. Several babies required more than one catheter during their course of total parenteral nutrition: in all, 41 were inserted. The site of entry was scalp vein in 19, antecubital vein in 19, and the long saphenous vein in three. The procedure from start to finish averaged about one hour. The mean line survival was 17 days, with a range of 6–45 days. The reasons for line removal were as follows: 25 electively at completion of total parenteral nutrition, seven occluded, four became infected, four were associated with limb swelling (including the three inserted from the leg), and one pulled out by the patient.

Failures

In six patients (16% of referrals) it was not possible to insert a line. In each case this was due to difficulties finding a suitable vein in sick babies who had already had a number of peripheral infusions. It is a useful rule for junior staff not to use antecubital veins for peripheral drips where possible if central venous feeding using this technique is anticipated. Quite a number of successfully catheterised babies had undergone repeated venepuncture, however, and careful inspection for unused veins is well worth while even in these circumstances.

Complications

Sepsis is the most common major complication seen with central venous feeding and occurred in four of our 31 patients. In each case the child became feverish and unwell without signs of localised infection. Positive bacterial cultures were subsequently obtained from both blood and the line once removed. The infecting organisms were *Staphylococcus aureus, Staph. albus, Streptococcus faecalis,* and *Klebsiella* species. These four patients all made an uneventful recovery after removal of the feeding line and treatment with antibiotics. We have compared patients with similar indications for total parenteral nutrition, underlying condition, and weight but fed either by surgically inserted central venous catheter or percutaneous line: the only significant difference in line performance with regard to days of use, blockage, sepsis, and accidental removal was a lower incidence of line associated sepsis in those patients with percutaneously inserted catheters.

Discussion

Percutaneous Silastic catheters are most suitable for small babies who are relatively immobile, less likely to pull on their lines, and with a total fluid requirement that can be accommodated by the flow restriction imposed by a 25G Butterfly (about 50 ml per hour). Clearly, their usefulness extends beyond the special care baby unit where they have been tried and tested. Central as opposed to peripheral feeding confers the advantages to the patient of not having painful, repeated, and increasingly difficult venous cannulation. Septic complications can be minimised by obsessive sterile nursing care.[6] The infusion system is changed daily by nurses who wear cap and mask; the disconnected Butterfly hub is soaked in 70% isopropyl alcohol together with the terminal attachment of the new system for three minutes before connection, a no touch technique being used throughout. Lines are dedicated to intravenous feeding fluids and cannot be used for giving drugs or taking blood.

To minimise the risk of producing limb oedema from constriction of venous return care should be taken when applying a circumferential Elastoplast dressing to start distally and work proximally, at the same time ensuring that the strapping is not tight. If a line is in place for some weeks and growth is taking place Elastoplast originally loose may become tight enough to cause foot or hand swelling. This will often resolve if the old strapping is replaced by fresh, loose tape. Tube gauze might be used as an alternative method of dressing to circumvent this problem.

Several advantages are apparent when comparing percutaneous insertion as described above with other methods of central venous catheterisation, not least the fact that it may be done at the bedside, without anaesthetic or surgical incision. The technique is simple to learn and, with practice, often quick to perform. Should the Silastic catheter be accidentally pulled out or disconnected, blood loss is unlikely to be severe due to its small bore. Line removal is simple, unlike with cuffed catheters (Broviacs, Hickmans), which become fixed by fibrosis and merit general anaesthesia for removal.

In our experience percutaneous insertion of Silastic central venous feeding catheters offers a simple and acceptable alternative to surgical line insertion in neonates and infants requiring total parenteral nutrition.

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Point of View

Case conferences—for child abuse

A cardinal recommendation of the Tunbridge Wells Study Group,[1] and now a pivotal part of widely followed procedures, is the holding of case conferences. These are immensely wasteful of professional time, and their only significant function can be to allay the anxieties of professional workers (and their realistic fear of being scapegoated), and there are better ways of doing this. Encouraging signs that a more critical attitude was beginning to be shown at one time towards case conferences and cognate activities by directors of social services departments [2] now seem to have lapsed. We agree with Geach[3] that case conferences are 'one of the most pernicious aspects of the procedures', and we strongly urge their abolition for the following reasons:

(i) Case conferences are dangerously irresponsible because they have no continued existence, and no one can be held personally accountable for their decisions.

(ii) Case conferences entail a gross breach of professional confidence; for it is naive in the extreme to accept the cosy assurances so readily offered that members of such an ad hoc gathering can trust each other. Caseworkers and clinicians are in any case not entitled to entrust to strangers the information they possess about their clients; and it is no part of a policeman's job to trust anyone, or to promise to respect confidences. 'Character assassination' may proceed without even the safeguards of a court of law; and the subsequent circulation of the minutes ensures an unrestricted and irrevocable dissemination of defamatory allegations.[3 4]

(iii) Case conferences are inherently ineffectual, because:

   (a) The crucial decision whether, and when, it is safe to allow the child to return to its parents is a technical decision requiring the highest degree of professional competence. It is as absurd to expect a case conference to judge the fitness of a parent to have a particular child as it would be for a physician to ask a committee of nurses, pharmacists, laboratory technicians and ambulance men to tell him how to treat a complicated case of diabetes.

   (b) Even if some of the individual participants should happen to be adequately equipped to make such a decision, it would be quite unrealistic to expect them to do so in such circumstances. The nature and degree of a parent's emotional problems and their probable response to treatment can be assessed only in the course of a personal diagnostic-therapeutic interview,[5] and not by any kind of debate, and still less by a debate arising out of differences of opinion that are inevitably based largely on emotional prejudices.

   (c) Decisions on the feasibility of treating parents' problems must also depend on the supervisor's knowledge of the treatment facilities available—including the abilities of the particular caseworkers willing to undertake the treatment, which it is obviously not proper to discuss in a case conference.

   (d) The decision cannot be made once for all. The supervisor must keep it continually under review.

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(This extract is taken from the policy document on child abuse written for the Society of Clinical Psychiatrists by M G T Chapman and A C Woodmansey with help from A Garwood, which appeared as a Supplement to the *British Journal of Clinical and Social Psychiatry,* June 1985 (Vol 3 No 2). It is reprinted with their kind permission.)

Archives of Disease in Childhood, 1986, **61,** 1142–1148

Correspondence

Nebulisers—uses and abuses

Sir,

Although I read the annotation on nebulisers by Drs Newman and Clarke[1] with considerable interest, I would like to make two critical comments.

Firstly, although they are right to emphasise the need for careful education to ensure the children do not place too much reliance on their nebulisers and delay seeking medical advice when their asthma is deteriorating, they fail to point out how useful a nebuliser can be in monitoring the progress of an attack. Parents are often reluctant to contact their general practitioner or take their child to the accident and emergency department unnecessarily and often ask for guidance on assessment of asthma severity. This can be provided by observing the child's response to inhaled beta$_2$ stimulants. If the child is dramatically or considerably relieved for at least two to three hours it is reasonable for the child to continue on his current treatment. If, however, the treatment with nebuliser fails to produce a considerable improvement or the child deteriorates within one to two hours then further help is urgently required.

My second point is that the authors claim that the doses delivered by nebulisers are large, assuming that all the active ingredient placed in the nebuliser is inhaled by the child. We know, of course, that this is untrue; at least ½ ml—that is, 25%—will remain in the nebuliser in droplet form. We also know that as the nebuliser is discharging throughout the respiratory cycle it is unlikely that even 25% of the remaining dose will penetrate the child's nose or mouth. Thus the dose reaching the lungs is likely to be in the region of 50 to 100 µg and not 250 to 500 µg as quoted in their paper. This is, of course, a trivial dose compared with that taken by many children in syrup or tablet form with complete safety.

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Dr Clarke comments:

Dr Milner's letter in response to our annotation makes two points. The first is that we failed to point out how useful a nebuliser can be in monitoring the progress of an attack and I am not sure the annotation was addressed to that specific aspect.

The second concerns the dose delivered by nebulisers. Approximately 10% of the dose placed in a nebuliser reaches the lungs and this we stated quite clearly, basing this figure on our measurements using radiolabelling techniques. For example, 2·5–5 mg of a bronchodilator liquid placed in a nebuliser would give on average approximately 250–500 µg in the lungs. This amount is only 10% of the original, partly because of the very factors that you mention—namely, some drug remains in the nebuliser and that inhaled by the patient is only during the inspiratory phase of the breathing cycle. It is quite invalid, however, to invoke the same factors to reduce the estimated drug delivery again by a factor of five to 50–100 µg. Furthermore, we certainly have not assumed that all the drug placed in the nebuliser is inhaled, either in our annotation or elsewhere. Of course there are other factors that may reduce the lung dose further, such as inefficient apparatus, large droplets that deposit in the mouth, a short nebulisation time, and patients using a mouthpiece but inhaling through the nose. These points merely emphasise the need to use nebulisers in a precise and efficient manner.

Nebulised pain relief for children

Sir,

I read your editorial on nebulisers with interest.[1] Sadly, there is no explanation given for their popularity with patients, which must in part be due to the fact that nebulisers give rapid effective relief of distressing respiratory symptoms without recourse to the needle. Children, like adults, dislike injections.

Other medications could similarly be given this way. For example, I have carried out research on adult volunteers and found that nebulisers can provide fast and effective relief of pain using morphine[2] and preferably diamorphine. (Masters NJ. Unpublished findings.) This use might be of value in paediatric casualty departments where in shocked patients intramuscular injections have poor absorption and intravenous delivery may be technically difficult to achieve. Could this warrant further study?

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Diagnosis of exocrine pancreatic insufficiency in cystic fibrosis by use of fluorescein dilaurate test

Sir,

Professor Cuschieri and colleagues suggest that use of fluorescein dilaurate in an oral pancreatic function test may, by detecting different levels of pancreatic function, differentiate between patients with cystic fibrosis who do not require exogenous enzyme supplementation and those who do.[1] The authors also propose the fluorescein dilaurate test as a screening test for pancreatic insufficiency to reduce the number of false positive diagnoses of cystic fibrosis. Examination of their data leaves me sceptical of these claims made on behalf of the test, for the following reasons.

(1) The implicit suggestion in this paper, that positive correlation of fluorescein dilaurate test result with faecal chymotrypsin value indicates this test to be semi-quantitative in assessing pancreatic function, is unsupported; I know of no evidence that faecal chymotrypsin correlates well with more direct measurements of exocrine state. Had faecal chymotrypsin values from the control group been presented, I suspect the overall correlation between faecal chymotrypsin and fluorescein dilaurate test result would have been very poor.

(2) The authors chose a cut off point of 20 for the fluorescein dilaurate test result, above which level gross pancreatic hypofunction was held to be excluded. A single patient with cystic fibrosis had a urinary fluorescein dilaurate value above this figure but also experienced no change in bowel habit once enzyme supplements were withdrawn. If, on further investigation, this patient was confirmed to have pancreatic sufficiency, the fluorescein dilaurate test as a screening test for pancreatic disease would seem to be no more sensitive than a clinical history of steatorrhoea. If, on the other hand, this same patient was shown indeed to have pancreatic insufficiency the fluorescein dilaurate test would have proved to be less sensitive than a simple measurement of faecal chymotrypsin, low in all the group with cystic fibrosis.

(3) We are told little about the controls other than that they were healthy. The fluorescein dilaurate test results show a very wide scatter (13·2–62·2), with three of the 15 giving values of 20 or below—that is, by the authors' criteria, indication for further investigation of pancreatic function. Used as a screening test for pancreatic disease, 20% false positive results give a specificity of only 80%. I wonder if the faecal chymotrypsin values in controls might have proved considerably more specific?

A simple, non-invasive test of pancreatic function with both high sensitivity (positivity in disease) and high specificity (negativity in absence of disease) together with the ability to delineate degrees of functional capacity must be considered yet to be found.

Reference

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Recurrent neural tube defects, risk factors and vitamins

Sir,

Wild and her colleagues conclude that the highly significant difference in recurrence rates of neural tube defects between mothers who took periconceptual vitamins and those who did not, in the study reported by Smithells and his colleagues, was due to vitamin supplementation.[1] They argue this on the basis that no significant confounding was found with certain factors such as social class or immediately prior miscarriage.

There are two problems with the paper. The first problem is that statistical re-analysis of the existing data cannot overcome bias that may have been introduced through patients presenting themselves and complying with supplementation being, in any case, at a relatively low risk of having a neural tube defect pregnancy. Allowing for known confounding factors cannot, of course, avoid bias from unknown ones. Although the authors conclude that bias from unknown confounding factors is unlikely to be of importance, we believe that in this particular instance it may have been critical. Most cases of neural tube defects, including recurrences, cannot be predicted by known means, indicating that the main risk factors are still unrecognised and could therefore exert a substantial confounding effect. Also adjusting for certain variables that *might* be confounding factors, but in fact were not, and then showing that adjustment for these variables did not alter the magnitude of the association is uninformative. It does not alter the strength of the evidence concerning whether the association was causal or due to bias.

The second problem relates to social class, and this has been the subject of previous publications.[2-5] One of us, with Professor Polani, has shown that some bias was introduced because, as expected, women in the vitamin supplementation group who took extra vitamins tended to be of higher social class than women who did not; they were also, by virtue of their social class, less likely to have a further pregnancy associated with a neural tube defect. We used data from the first cohort of pregnancies in the vitamin supplementation study conducted by Smithells and his colleagues. In a letter replying to our paper they said that if data from both the first and second cohorts were aggregated no social class confounding was evident (the conclusion that Wild and her colleagues reach again in their present paper). Our response to the letter still applies—namely, that for there to be no bias in the first and second cohorts combined, women of relatively high social class in the second cohort must have had a *high* risk of neural tube defect recurrence, a surprising result that is contrary to knowledge of the epidemiology of the disorder. Indeed, the opposite effects in the two cohorts are extremely unlikely to have arisen by chance. The relative risk of having a neural tube defect pregnancy for 'low' social class women compared with 'high' social class women was 2·98 in the first cohort and 0·19 in the second, after allowing for supplementation (p=0·003). This apparently inconsistent result between the two parts of the study needs to be explained before it can be concluded that, on average, social class was not related to neural tube defects and so could not have biased the results.

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[3] Wald NJ, Polani PE. Neural-tube defects and vitamins: the need for a randomized clinical trial. *Br J Obstet Gynaecol* 1984;**91**:516–23.

[4] Smithells RW, Sheppard S, Wild J, *et al.* Neural-tube defects and vitamins: the need for a randomized clinical trial. *Br J Obstet Gynaecol* 1985;**92**:185–6.

[5] Wald NJ, Polani PE. Neural-tube defects and vitamins: the need for a randomized clinical trial. *Br J Obstet Gynaecol* 1985;**92**:187–8.

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Drs Wild and Sheppard and Professor Smithells comment:

The points raised by Professor Wald and Dr Thompson have been raised and responded to in the papers they cite and elsewhere. Further reiteration would not be helpful, but we must again refute their inaccurate statement that our observations on social class and recurrence of neural tube defects are 'contrary to knowledge of the epidemiology of the disorder'. We are aware of only one published study of *recurrence* of neural tube defects by social class.[1] This showed a lower recurrence rate in classes I + II than in III + IV + V, but the difference was not significant.

Wald and Thompson believe that 'the main risk factors (for neural tube defects) are still unrecognised' but are curiously reluctant to consider, on the evidence, that vitamins might be one of them. We quite understand, however, that Professor Wald is not open to persuasion in this matter and we wish him all success in his own study.

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Plasma zinc concentrations in iron supplemented low birthweight infants

Sir,

We were interested to read the recent paper by Salvioli *et al* on plasma zinc concentrations in iron supplemented infants.[1] It is indeed an interesting question whether low birthweight babies fed an iron fortified formula need additional iron. The authors conclude that they do, but we wonder whether a difference in mean haemoglobin of 9 g/l is important and whether a haemoglobin <110 g/l signifies anaemia in the first year of life. The study was not a randomised trial; one group received iron supplements for more than five months, whereas the other group had not received iron supplements for three months but could have previously for up to nine months. The authors also address the question of whether iron supplements influence plasma zinc concentrations and imply that plasma zinc concentrations reflect zinc state or nutrition. This is an incorrect assumption as plasma zinc is highly influenced by recent dietary intake, stress, the metabolic state of the patient, postnatal age, and a diurnal variation. It is not mentioned when, in relation to feeds or iron supplements, the blood samples were taken.

A ratio of inorganic iron:zinc greater than 2 has repeatedly been shown to influence zinc absorption. It is likely that the zinc absorption in their infants, who received iron and zinc in a 5:1 ratio, would have been reduced. Whether this is important, however, remains to be shown. We feel that it should be made clear that the authors were not studying zinc state or zinc absorption but only plasma zinc concentrations. The importance of their findings is unclear and surely does not reassure us that iron supplements do not influence zinc metabolism.

Reference

[1] Salvioli GP, Faldella G, Alessandroni R, Lanari M, Benfenati L. Plasma zinc concentrations in iron supplemented low birthweight infants. *Arch Dis Child* 1986;**61**:346–8.

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Dr Salvioli comments:

The only purpose of our study was to determine whether administration of high supplemental iron to low birthweight infants might result in zinc deficiency, as manifested by a decrease in plasma zinc.

According to Yip *et al,* although serum zinc is not a reliable indicator of zinc nutrition in individuals, it probably provides useful information for groups of subjects.[1]

Thus the equivalent plasma zinc concentrations found in two groups of low birthweight infants, comparable in all but the amount of iron supplement, reassures us that long term iron supplementation is not associated with evidence of compromised zinc nutrition.

Concerning the question of whether low birthweight infants fed low iron fortified formula need additional iron, we can state that the stopping of medicinal iron supplementation determines even after three months the negativisation of iron balance and a significant reduction of haemoglobin concentration.

Reference

[1] Yip R, Reeves JD, Lonnerdal B, Keen CL, Dallman PR. Does iron supplementation compromise zinc nutrition in healthy infants? *Am J Clin Nutr* 1985;**42**:683–7.

Medical care in severe mental handicap

Sir,

Your leader in the June *Archives* is most timely.[1]

Under 'Management issues' the opening sentence is 'Community care for children with severe handicap is largely parent care'. This of course is totally true, and I think we should underline that in a sense our first responsibility to these severely handicapped children is regular concern for the parents who do the caring. These parents work more hours than any professional is asked to do and carry loads that no professional would be asked to carry.

Later, in the same paragraph, there is reference to the fact that 'there has been some debate as to whether parents should be persuaded to use such facilities'—that is, respite care, etc.

May I suggest that we have an absolute obligation to persuade parents and indeed 'sell' the use of such facilities. Appropriately, our immediate response to the birth of a handicapped child is to press for bonding, and we have all noticed the large number of parent carers of the severely handicapped who become overprotective. Perhaps we should interpret this in terms of the parents following our advice about bonding too fully.

Normal children take the initiative and spontaneously de-bond, but with the severely handicapped this does not happen and if there is to be any 'real normalisation' then the parent has to initiate the de-bonding.

The deeply caring mother of the severely handicapped child sees her child as needing her more than any other child in the family and I believe needs specific help to see that:

(a) the handicapped child will not take the initiative to de-bond;

(b) it is in the interest of the child for the parents to initiate de-bonding;

(c) there is a major bonus for the parent who allows this to happen—within the context of respite care—as she will also be looking after herself and thus be able to continue caring for the severely handicapped child.

The need to care for the parent carers and our need to 'sell' the use of respite care, perhaps particularly in the preschool period, should perhaps be given an even higher profile.

Reference

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Bereaved parents and the ethics of neonatal care

Sir,

Two articles in a recent *Archives* are complementary and deserve comment. Newton, Bergin, and Knowles tell of the benefit to bereaved parents and insight gained by staff on meeting to discuss a child's death.[1] This is a lead for all who care for dying children. Those who offer to see the parents of babies such as those described by Bissenden[2] find that what paediatricians deem to be poor quality lives parents perceive as having unique value.

The 'overall moral view' of our society is neither consistent nor inspiring. Whether we consider abortion on demand or provision for the mentally ill and elderly, expediency dominates but is no guide for us. If, instead, we as a profession were to hold an unshakeable regard for life's *value*, this need not always mean the full parade of the machinery of life support but would always mean trying to improve the *quality* of life (for both baby and parents) by being ready to offer palliative and terminal care. To agree to abolish the phrase 'non-treatment group', rather than agreeing to abolish any babies, would clarify the important moral distinction that does exist between stopping aggressive treatment and killing. When this is clear to the parents bereavement interviews go better. When we make it clear to the public we may start to influence society's views rather than being insidiously swayed by them.

References

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[2] Bissenden JG. Ethical aspects of neonatal care. *Arch Dis Child* 1986;**61**:639–41.

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Neonatal tuberculosis

Sir,

We were interested to read the short report by Bate, Sinclair, and Robinson as it reminded us of a similar case, previously unreported, seen by us some years ago.[1]

A baby girl was delivered by forceps at 36 weeks' gestation to a 19 year old married primigravida, who was a Spanish hotel waitress. After a normal pregnancy she was an emergency admission with what seemed initially to be a pyogenic meningitis but was subsequently shown to be tuberculous meningitis, although culture for acid fast bacilli yielded negative results. Her uncle had almost certainly died from pulmonary tuberculosis.

The baby was separated from her mother at birth in good condition but became jaundiced, with a maximum serum bilirubin concentration of 190 μmol/l on the fourth day. She failed to thrive, developing a series of staphylococcal infections followed on the 22nd day by a fever of 38°C (rectal), pulse 140–172/min, irregular respirations averaging 48/min, fine crepitations in the right lower zone, and moderate hepatosplenomegaly. A chest *x* ray film (Figure) showed extensive coarse miliary mottling due to miliary tuberculosis. Scanty acid fast bacilli were identified on the Ziehl-Nielsen film from gastric washings, and subsequently *Mycobacterium tuberculosis* was grown on culture. Treatment was started with rifampicin 10 mg/kg/day, isoniazid 20 mg/day, and prednisone 2 mg/kg/day, and she began to gain weight slowly and was well on discharge aged 5 months, soon afterwards emigrating with her mother to Caracas, Venezuela, where she was thriving at 13 months.

Our case shows features of the 'aspiration' type of congenital tuberculosis, as opposed to the 'haematogenous' transplacental type,[2] with infected amniotic fluid entering the fetal lungs, probably intrapartum,[3] and is unusual in that both mother and baby survived.

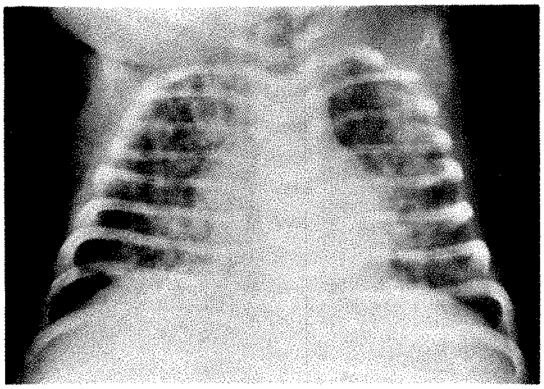

Figure *Chest* x *ray of the case aged 1 month, showing extensive bilateral miliary mottling due to miliary tuberculosis.*

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Height measurements at the onset of acute lymphoblastic leukaemia

Sir,

I read the article by Bessho with interest.[1] The author could not find significant height differences between children with acute lymphocytic leukaemia and healthy controls matched for age and sex. This indeed is remarkable, for most other investigators have claimed the opposite, leukaemic children being taller than controls. Yet I am not convinced for the following reasons.

It is known that severe illnesses result in a decrease in growth velocity. This has been investigated also in the case of acute lymphoblastic leukaemia by Berglund *et al.*[2] The authors observed a decrease in growth before the start of treatment and suggested that the disease might cause the growth failure. Most interestingly, they not only compared height with a reference group at the clinical onset of the disease but also one year before diagnosis. Thus I am sceptical indeed whether single measurements of body height at the instant of the diagnosis of acute lymphoblastic leukaemia in fact represent valid information on growth. Could pre-existing tall stature have vanished by the time of the diagnosis?

Though the role of growth hormone as cited by Bessho is indeed questionable, there is overwhelming evidence for the involvement of polypeptide growth factors not only in the regulation of normal growth but also in growth factor initiated pathways in the aetiology of cancer.[3]

With respect to this, child growth before the onset of acute lymphoblastic leukaemia is an interesting variable. Bessho's patient group is very large and obviously well matched with its controls. I would like to know more about the patients' growth, not just mean height at one point of their development.

References

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[3] Goustin AS, Leof EB, Shipley GD, Moses HL. Growth factors and cancer. *Cancer Res* 1986;**46**:1015–29.

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Dr Bessho comments:

I do not deny the importance of information about the height and its velocity before the onset of acute lymphoblastic leukaemia and the possibility that height at diagnosis may be a function of growth enhancing effect of possible growth factor(s) and growth suppressing effect of the disease (acute lymphoblastic leukaemia). It is worth while to confirm Dr Berglund's finding as a phenomenon with a larger scale study using an appropriate control.

I do not think, however, that this kind of study could clarify the possible role of growth factor(s) on leukaemogenesis. No one can solve single equations with two or more variables. Obviously, other kinds of studies are required for this purpose. Therefore, I carefully avoided making the statement that growth hormone had no role concerning leukaemogenesis.

Congenital anomalies associated with hypothyroidism

Sir,

The report by Bamforth and colleagues of a high incidence of various extrathyroidal abnormalities associated with congenital hypothyroidism detected by neonatal screening[1] is of interest as it could throw new light on the aetiology of these congenital malformations. Such an association had been suggested in infants with congenital hypothyroidism detected on the basis of clinical signs before the era of screening[2] but has not been reported in large series of hypothyroid infants detected by screening.[3]

In a series of infants similar to the one of Bamforth *et al* we could not confirm their findings: since the introduction of neonatal thyroid screening in Belgium in 1974, our own centre has screened 125 257 infants and has detected 41 infants with persistent primary hypothyroidism—that is, an incidence of 1/3055. Only one of them had associated anomalies: this girl was born after a normal pregnancy of 38 weeks' gestation, with biological signs of severe congenital hypothyroidism (serum thyroid stimulating hormone at diagnosis 100 mU/ml and thyroxine 69 nmol/l). Thyroid scintigraphy showed a lingual thyroid gland. A colic duplication, suspected by antenatal echography at 3 weeks' gestation, was confirmed by operation on day 7. On day 17 she had a second abdominal operation for hypertrophic pyloric stenosis. Further history has been uneventful.

This association could be explained by a simple embryological mechanism as the development of the thyroid gland (formation and migration between 16th and 50th day of fetal life) and the gut (formation and rotation of the umbilical loop between 21st and 42nd day) both occur early in the fetal development.

The question arises as to whether the results reported by Bamforth *et al* could represent the consequences of local genetic or environmental factors, or both. As suggested by the authors, this point deserves further investigation.

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Endotracheal suction techniques in the neonate

Sir,

Endotracheal suction of the ventilated neonate is often performed during neonatal intensive care. It has many side effects, including hypoxia, increased blood pressure and cerebral blood flow velocity,[1] and atelectasis.[2] In an attempt to reduce side effects many neonatal units have developed special procedures to achieve efficient suction in the shortest possible time. In one such technique the endotracheal tube suction catheter is attached to a mucus extractor and suction applied by the nurse rather than by the traditional wall mounted vacuum source with a gauge.

We investigated the pressures generated by this technique. The patient end of a mucus extractor was attached directly to a water manometer. Four doctors and six trained experienced nurses were then asked to apply suction without being able to see the pressures generated. When asked to 'suck out vigorously' the maximum pressure achieved ranged between 84 and >250 cm H_2O, median 147 cm H_2O. Each individual was able to sustain his or her *maximum* pressure for approximately five seconds in the closed system, which allowed no gas flow once peak pressures were achieved.

Each individual was informed of his maximum and then asked to suck at a pressure of 20 cm H_2O, still blind to the manometer readings. The pressures generated ranged between 27 and 107 cm H_2O, median 43·5 cm H_2O. Participants then practised sucking out to 20 cm H_2O while watching the manometer before repeating the suction blind. They achieved pressures ranging from 9 to 52 cm H_2O, median 18 cm H_2O. None could maintain a constant pressure for more than two seconds in this situation.

We therefore conclude that endotracheal suction through a mucus extractor is inadvisable. Without a gauge certain individuals generated very high negative pressures when sucking vigorously. These high pressures could result in atelectasis and profound circulatory disturbances. At lower pressures, the variation in suction from second to second rendered suction inefficient and could lead to inadequate maintenance of the airway.

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Haemophilus influenzae type b meningitis resistant to ampicillin and chloramphenicol

Sir,

Guiscafré *et al* report two cases of meningitis due to *Haemophilus influenzae* type b resistant to ampicillin and chloramphenicol.[1] They comment on the recent emergence of such strains and recommend that third generation cephalosporins such as cefotaxime or latamoxef should be considered the drugs of choice in the treatment of such cases.

We have reported[2] a 3 month old infant with *H. influenzae* type b meningitis and ventriculitis who failed to respond to high dosage of chloramphenicol, ampicillin, and latamoxef in succession but whose infection resolved promptly with the addition of rifampicin. We consider that rifampicin should be one of the drugs of choice in haemophilus meningitis not responding to chloramphenicol and ampicillin, as resistance is rare and speed essential.

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rchives of Disease in Childhood, 1986, **61,** 1149–1150

Book reviews

ssential Allergy. By N Mygind. Pp 480: 6·50 paperback, Blackwell Scientific, 86.

ere is no shortage of books on allergy. e standard multi-author volumes (often merican) tend to be good encyclopaedias t fail to give practical advice. 'Essential llergy', however, is a landmark not only the field of allergy but also in setting a w standard for clarity of writing and esentation. The innovative format of this ok could well be applied to many other edical topics.

There are 107 short mini chapters. tentially awkward subjects, most no- bly immunological mechanisms, are pre- nted in beautifully lucid small and easily gestible parts. The layout, diagrams, ustrations, and tables are models of rity. The author has selected key refer- ces, given a short description of the ntent, and added his own helpful and itical remarks. These references appear small print near the end of the chapter, d each chapter concludes with a mmary. This structure means that the ok will be useful to the student and ecialist alike, for it can be read at fferent levels. I found it particularly eful to be able to refer to key research d clinical studies that form the basis for rrent knowledge and practice.

The content is as original as the layout. he mini chapters are divided into 12 ctions, on basic immunology, allergen urces, the diagnosis of allergy, gastroin- stinal reactions and food allergy, rhinitis, e disease, skin disease, environmental ntrol and immunotherapy, systemic lergic reactions, two sections on asthma, d one on other lung diseases. Through- t are numerous difficult areas and prac- al problems that have never really been ell described before. In particular, the ok covers *all* the practical aspects of eatment of atopic disease. The author scusses every form of treatment, so that tihistamines, bronchodilators, corticos- roids, allergen avoidance, and hyposensi- sation are all fully discussed. The author's lanced but critical approach is an invalu- le ingredient. Thus, to take one of many ssible examples, the doctor looking for idance on how to treat atopic eczema ill find a particularly good account of topical treatment as well as clear and balanced advice on the role of elimination diets and allergen avoidance. Indeed, the book is worth having just for its excellent description of the standard medical treatment of asthma, eczema, rhinitis, urticaria, and allergic conjunctivitis, all of which are more clearly presented here than in most paediatric textbooks.

This magnificent book totally succeeds in its aim of being suitable for the student, postgraduate, and specialist alike. It is easy and enjoyable to read and is reasonably priced. I think it will also interest those who in the past have been put off by the indigestible nature of immunology and the hopelessly anecdotal nature of much current allergy practice. One subject not covered in this book is drug allergy. The difficulty of getting sound practical advice from colleagues on this complex topic is matched by a dearth of useful publications.

T H DAVID

Pediatric Respiratory Therapy. 3rd ed. By M D Lough, C F Doershuk, R C Stern. Pp 300: £28·50 hardback. Blackwell Scientific Publications, 1985.

The subject matter of this book ranges from the development of the respiratory system through various theoretical and practical aspects of neonatal and non-neonatal respiratory care to an analysis of the importance of pulmonary function and exercise tests. This is the third edition (the first was produced in 1973) and the considerable clarity of the text reflects this. The style is North American and the text appears to be specifically designed for paediatric respiratory therapists, who do not exist as a single entity on this side of the Atlantic. The authors attribute a considerable portion of the improvement in paediatric respiratory care in North America to the formal organisation of respiratory therapy services around such a person. It is an intensely practical book with plans of management, checklists, flow charts, guides to help in the choice of equipment such as endotracheal tubes, and normal ranges for respiratory function tests. I particularly liked its large section on mechanical ventilation. There are roughly 400 references and helpful suggestions with regard to further reading at the ends of the chapters. A modest index is present.

There are a few negative features. Mist therapy is advocated more enthusiastically than we would do in Britain. Details of instructions and equipment reflect the North American market from which the apparatus was purchased. There are occasional lapses from firm management plans as in the failure to advocate a definite plan in airway occlusion caused by a foreign body. Tuberculosis does not appear to be mentioned in the text or index.

This is a book that should take its place (for reference) in the paediatric respiratory ward or intensive care unit where the physiotherapist, nursing and physiological measurement technicians, as well as the junior medical staff would find its highly practical approach of considerable value. Perhaps the integration of practical paediatric respiratory therapy in the hands of an ancillary worker, as assumed in this text, might be usefully considered for the United Kingdom.

FLEMING CARSWELL

Lysosomal Storage Diseases: Biochemical and Clinical Aspects. By R W E Watts and D A E Gibbs. Pp 284: $35·00 hardback. Taylor and Francis, 1986.

The biochemical background, classification, and presentation and clinical management of the lysosomal storage diseases represent areas of difficulty for the average practising paediatrician. The stated aim of the authors of this book is to give an up to date account of this major topic, and in this objective they have succeeded admirably. This is not a book to be purchased by every paediatrician in training nor indeed for the established paediatrician. It is, however, essential reading for anyone who is confronted with the practical management of a child suffering from a lysosomal storage disease.

In this book is to be found a concise review of the biochemical and genetic background to the disorders, which is then followed by detailed discussion of the sphingolipidoses, the mucopolysaccharidoes, the glycoproteinoses, mucolipidoses, together with acid lipase deficiency diseases and glycogenosis type II.

The penultimate chapter deals in a clear manner with the general approach to the treatment of lysosomal storage diseases, the final chapter being a 'Look to the Future'.

Thoroughly recommended!

A AYNSLEY-GREEN

A Classified Bibliography of Controlled Trials in Perinatal Medicine 1940–1984. Prepared by the National Perinatal Epidemiology Unit. Pp 414. Oxford University Press, 1985.

This book is a directory of those perinatal research studies that have sought to compare alternative care strategies and have used randomisation to avoid or minimise selection bias. The 2770 studies selected therefore represent the best guide to practice available from the published reports, and it is extremely useful to have the references brought together in this way. The classification and layout, once understood, make it reasonably easy to find the references dealing with any particular question. I am sure anyone working in the perinatal field will want to have access to a copy.

P R F DEAR

Handbook of Endocrine Tests in Children. Edited by I A Hughes. Pp 141: £9·95 paperback. John Wright and Sons, 1986.

The interest in paediatric endocrine conditions has steadily increased over recent years, with a consequent increase in endocrine testing in children not only in specialised endocrine units but in many general paediatric units and on occasions, with the older child, in mainly adult units. There is a bewildering array of tests available and therefore a clear need to limit and select the endocrine tests most appropriate for the individual child.

This excellent book by Dr Hughes can truly be regarded as a handbook and fulfils a very great need on the paediatric ward and will be of great help to paediatric junior (and senior) medical staff.

The introductory chapter is brief but discusses adequately the general principles of endocrine testing in children. The main body of the book consists of a description of the various endocrine tests applicable to each endocrine gland, with clear instruction about performing the test and then a much needed paragraph on interpretation of the results. This is followed for each endocrine gland by a series of case illustrations, with a short case history followed by relevant investigations and comment. The case illustrations are chosen to cover common clinical presentations in paediatric endocrinology that may have similar clinical features but the results of wisely chosen endocrine tests may suggest different diagnosis.

The book is completed with an appendix of normal values for the various endocrine tests.

I am sure that this handbook will be popular and should find a place on every paediatric ward likely to be involved in endocrine testing. The format of the book should appeal to junior paediatric staff and also undergraduate medical students. Endocrinology is a rapidly changing field and perhaps a further edition will be necessary in a few years to update the various endocrine tests and protocols.

C S SMITH

Hyperkinetic Children: A Neuropsych social Approach. By C K Conners a K C Wells. Pp 160: £10·00 paperba £19·75 hardback. Sage Publications, 198

This book is number seven in a worthwhi series on developmental psychology a psychiatry. It is written by Americans w have contributed extensively to the fiel In particular, the Conners scale is a wide used instrument for assessing hyp activity.

The book provides a comprehensive a readable account from a mid-Atlantic pe pective of research and theoretical aspec It is directed towards the researcher child psychopathology rather than t paediatrician interested in keeping up date in the field.

NAOMI RICHM

Childhood Asthma—What it is and wh you can do. By N Buchanan. Pp 9 paperback. Doubleday, 1986.

This paperback book is intended to expla asthma to parents who are concerned the child might have the condition and to tho parents seeking further information abo their child's diagnosis. The topics cover are admirably wide, but some suffer fro lack of detail. Written in Australia, lowance has to be made for giving on addresses of Antipodean Asthma Associ tions, but the importance of maintenan treatment could be amplified and it shou be explained that beclomethasone is steroid.

The friendly type and pleasant illustr tions made easy reading, while the conten are reassuring and 'middle of the road Parents looking for general information asthma would find it in this book and m be prompted to ask more questions of the doctor after reading it.

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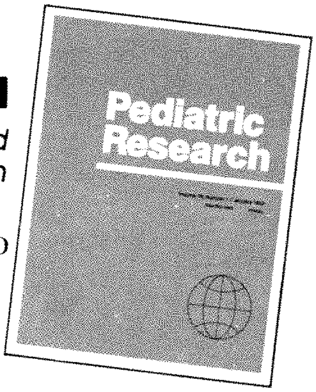

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134. Band
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September 1986

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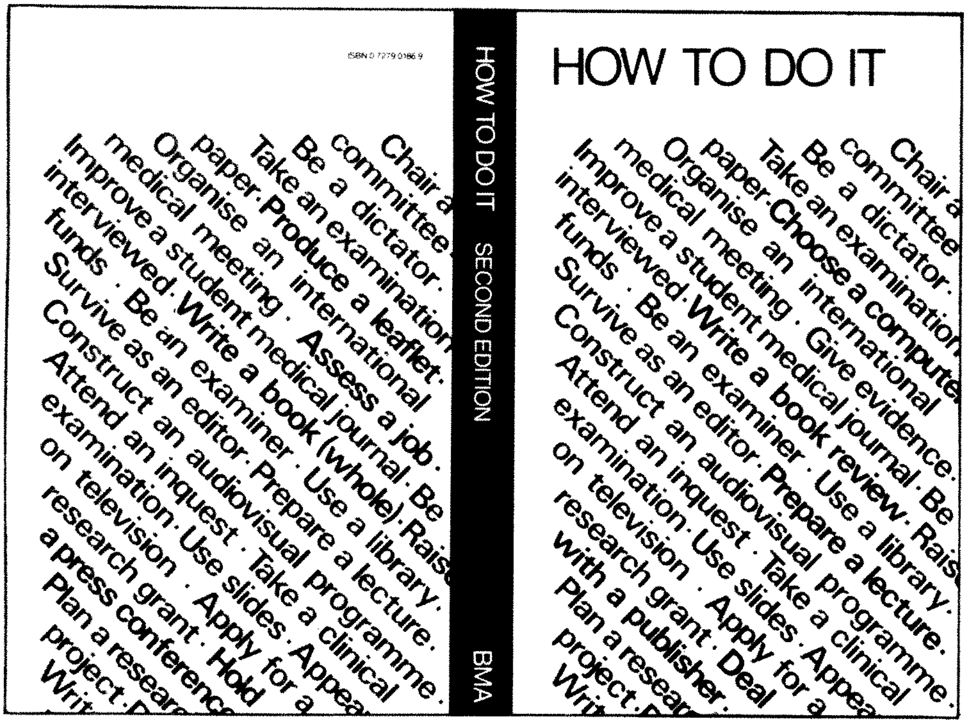
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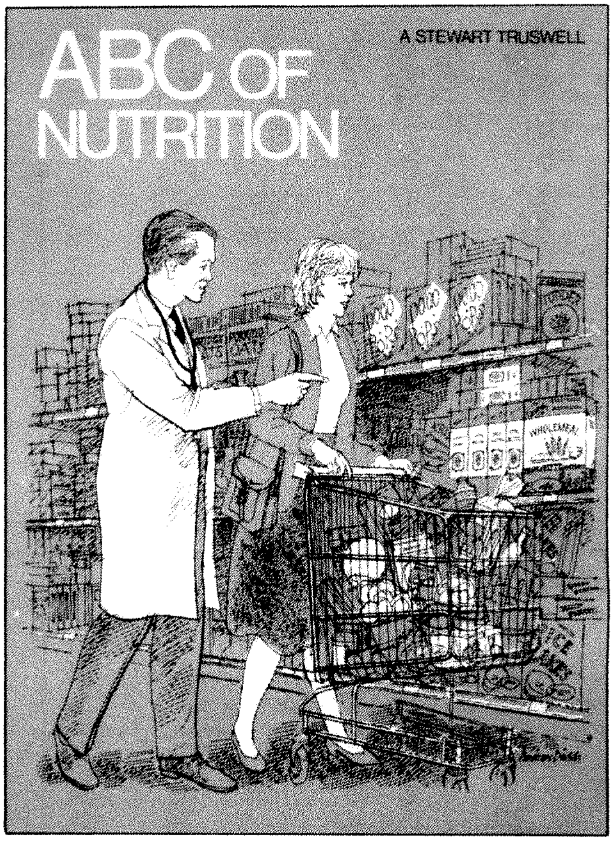

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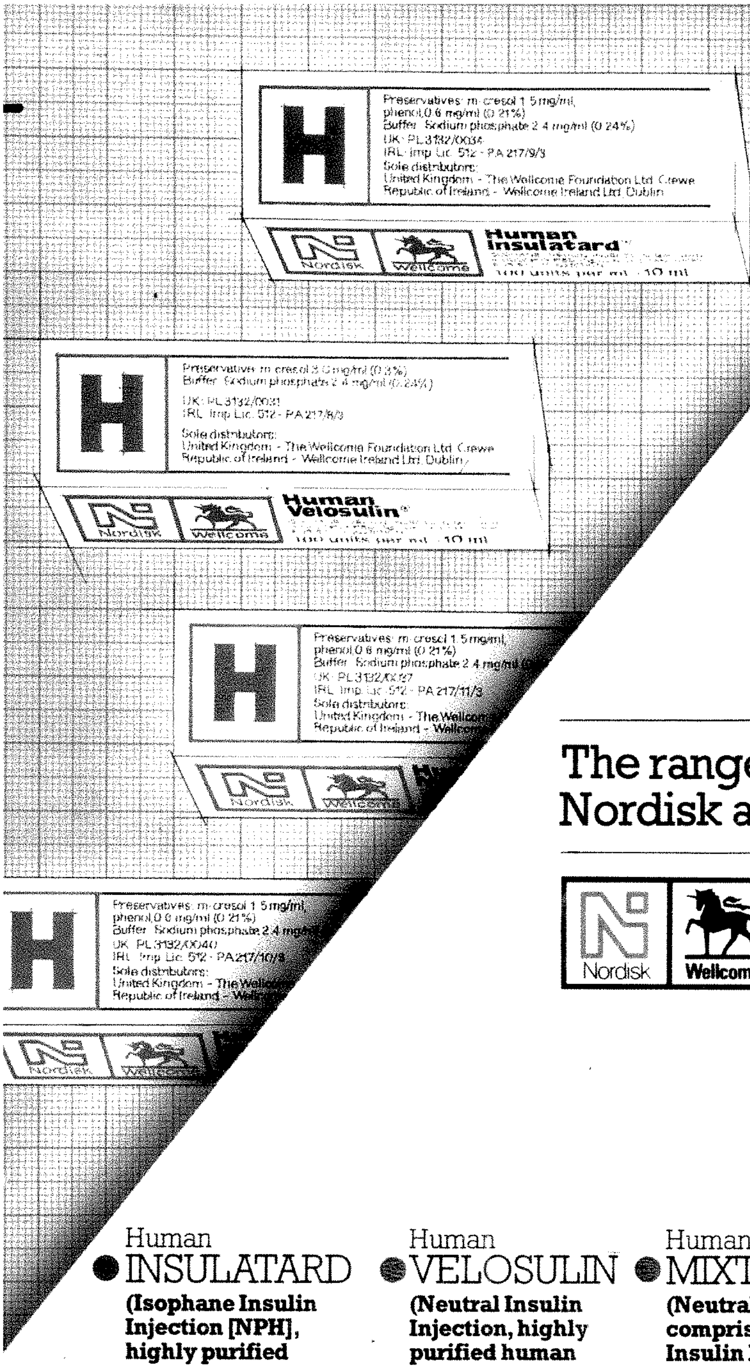
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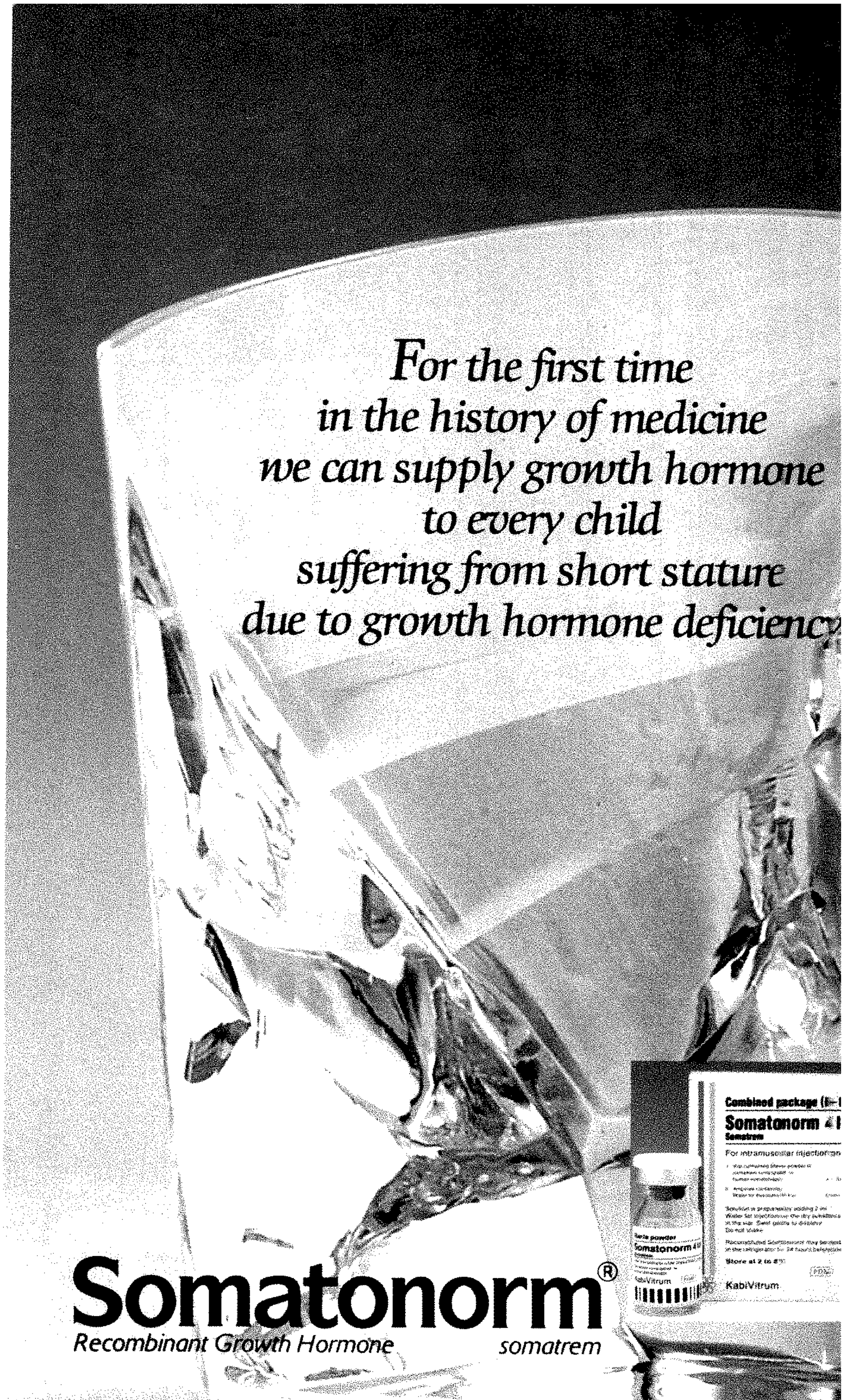

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Thalassaemia and Haemolytic Anaemias, Gene Probes, Leukaemias, Bone Marrow Transplants in Childhood, Coagulation Disorders

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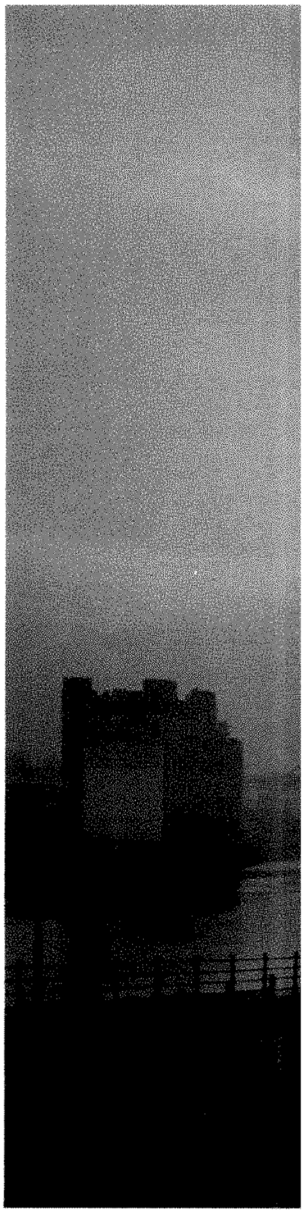

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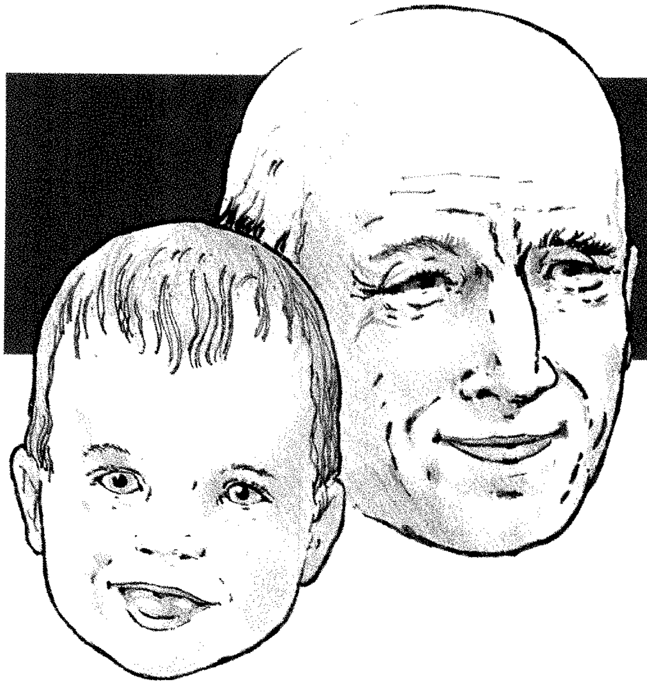

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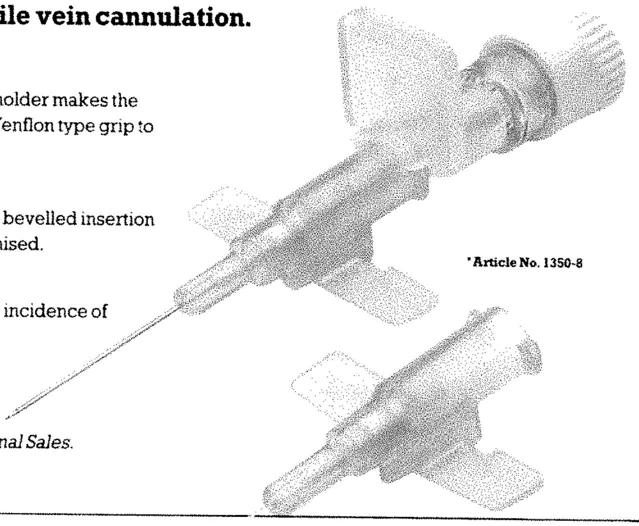

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Archives of Disease in Childhood, 1986, **61,** 1151–1152

Annotations

Anaemia and child health surveillance

Malnutrition has been a world problem throughout the ages. Lloyd de Mause, in his 'History of childhood', traced many of the causes from the deliberate restriction of food for young Spartans in Plutarch's time to make them physically strong to prolonged breast feeding with late weaning at 1 to 3 years of age in the 12th and 13th centuries and the use of starvation for punishment in the Middle Ages—a form of child abuse.[1]

In more recent times Helen Mackay in her classical paper in the third volume of this journal, published in 1928, studying 541 east London infants, with 2561 haemoglobin estimations, wrote that 'the great majority of artificially fed and many breast fed infants in London are anaemic'[2]—due to iron deficiency. There have been hundreds of subsequent studies. Edward de Lobo, in another classical book, found that 24% of 3 year olds born to mothers of Asian origin in Luton had a haemoglobin concentration of less than 70% (10 g/dl).[3] He ascribed this to prolonged milk feeding, delayed weaning, and other dietary customs. Willoughby wrote that a Glasgow survey of 6 to 24 month old children revealed a mild degree of iron deficiency in 32% of unselected children but in 59% of children in Glasgow slums.[4]

There are many reasons for the worldwide problem of anaemia. Apart from poverty, they include chronic infection, especially malaria, worms, and chronic dysentery; sickling (especially American negroes, Indians, and Africans); thalassaemia (in Mediterranean countries, India, and Sri Lanka); and glucose-6-phosphate deficiency (Greece, Turkey, China, India, and Philippines). Lead poisoning by contamination of water and foodstuffs and other sources, is a worldwide cause of anaemia: de Lobo notes that whereas lead sulphide in eyelid cosmetic paste (Surma) favoured in Bangladesh and elsewhere is banned in Britain, travellers returning from Bangladesh may bring it into Britain; the lead is washed by tears into the eyes, nose, and thence the alimentary tract, where it is absorbed.[3] Many studies have reviewed the risks of nutritional deficiency in vegetarian and especially the Zen macrobiotic diet used by families of Asian origin.[5-7]

Iron deficiency may also result from maternal anaemia in pregnancy, preterm delivery, infections, malabsorption, general malnutrition, and blood loss. Several papers have ascribed iron deficiency anaemia to blood loss resulting from allergy to cow's milk protein,[8 9] and it was suggested that pasteurised cow's milk should not be given in the first six months. In one study occult gastrointestinal bleeding due to allergy to cow's milk protein was found in 17 of 34 infants with iron deficiency anaemia.[10] Blood loss may result, among other causes, from haemophilia, ulcerative colitis, hiatus hernia, or the use of aspirin and non-steroidal anti-inflammatory drugs.

The relation of iron deficiency to pica is uncertain. Pica is usually associated with iron deficiency, but it is not clear which is the primary cause[11] and there are commonly other socioeconomic problems,[12] such as neglect, child abuse, and abnormal parent-child relationships.

The effects of malnutrition and iron deficiency have been extensively studied in Mexico, South America, United States, South Africa, and Britain. I have very briefly summarised this work.[13]

Iron deficiency has been said to cause defective physical growth,[14] delayed language and cognitive development,[15] the attention deficit disorder, impaired school performance and clumsiness,[16] and immunological deficiency with consequent repeated infections.[17] Two reports from Java and Egypt found that iron deficiency reduced the learning problem solving capacity of schoolchildren.[18] Oski, in a series of papers in several American journals, showed the effect of treatment with iron on improving the behaviour, cognitive skills, and general learning ability in children with iron deficiency.[19]

In this journal a Birmingham team in a well planned double blind randomised intervention study of 97 toddlers with anaemia showed a direct relation between iron deficiency, physical growth, and delayed psychomotor development.[20] Their conclusion, that while iron deficiency may not be the only factor in impaired development it can at least be readily identified and treated, is important and deserves emphasis. They add that child health clinics should hunt out and treat iron deficiency in toddlers as part of routine child health surveillance. I would add that all child health clinics should have facilities for haemoglobin estimation. It is difficult to detect minor but important degrees of anaemia in coloured children, and haemoglobin estimation should be routine in all of them—and in those of ethnic backgrounds at special risk of anaemia, nutritional or otherwise.

Anaemia is common in mothers, and their anaemia may have an appreciable effect on their well being and tolerance of their children's difficult behaviour. It is not enough to treat a child's anaemia and ignore that of his mother. Child health surveillance should include checking for anaemia.

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Sweetness

Sweetness is one of the so called basic tastes (sweet, sour, salty, and bitter). In other words, it is a gustatory experience devoid of olfactory or tactile elements. It is also hedonic and attractive, though this depends on the concentration of stimulus. Although most of the sweetness in our foods comes from sugars (mainly sucrose) and is therefore nutritive,[1] several thousand non-nutritive sweeteners are now known. The advantage of these latter types is that they are metabolically inert or make an unappreciable contribution to energy intake. Some are therefore useful for dietetic or diabetic foods and cheap (on a sweetness basis) compared with sugars. Sugars provide bulk, mouthfeel, and osmotic pressure (preservation power) in foods. Legally in the United Kingdom, however, they are not classed as sweeteners. Since 1983, 12 sweeteners are permissible for use in foods in the UK (Table),[2] divided into six bulk sweeteners—that is, hydrogenated sugars or polyols—and six intense sweeteners.

The bulk sweeteners are of about the same sweetness as sucrose (cane or beet sugar), whereas the intense sweeteners are hundreds or thousands of times sweeter. A recent conference organised by the International Life Sciences Institute at Geneva was devoted to chemical, psychophysical, sociological, and dietary aspects of sweetness.[3]

Although the desire for sweetness may be enhanced by overindulgence, the recognition of sweetness and its enjoyment seem to be inborn. Steiner has shown that human neonates display positive—that is, a relaxed satisfied smile—gustofacial responses to sweet solutions, easily distinguished from the responses to other basic tastes.[4] Engen points out that taste elicits more definite hedonic reactions than odour in the newborn, as well as in children 3–7 years old.[5] It is therefore interesting that, although olfaction is normally considered to dominate gustation in flavour perception, taste may emerge as an earlier signal of what is ingested. The human infant is equipped with taste buds located in the tongue papillae, and some of these are present on the lips and even possibly the cheeks. Those outside the oral cavity decline in numbers with increasing age of the child; each taste bud contains about 60 taste cells on which are the receptors for all four basic tastes. The life span of a taste cell is about 10 days.

Basic chemoreception of sweetness

Sweet molecules may be either large—for example, proteins—or quite small—for example, simple sugars, polyols, and certain salts. Sweetness is thought to originate in a loose binding of a stimulus molecule with a receptor. The mechanism of this binding is probably hydrogen bonding, and a steric fit of stimulus molecule with receptor protein is therefore a necessary preliminary to an action potential at the taste neuron. Why then do some molecules taste thousands of times sweeter than the sugars? The answer seems to be twofold. Either the intense sweeteners accede better to receptors or they activate them better due to a better steric fit. Some molecules may do both, and a clue to the mechanism of sweet chemoreception comes from the peculiar temporal properties of many modern sweeteners. Intensely sweet substances seem to have a slow 'reaction time'—that is, time for the onset of sweetness sensation after tasting—and a pronounced persistence—that is, duration of taste. The new protein sweetener thaumatin, for example, persists for 20 minutes or more and is therefore quite unsuitable for use in foods as such. On the other hand, it is useful in chewing gum and medicines where it effectively masks other unpleasant tastes. Persistence is very likely caused by some organised, localised concentration of stimulus molecules at or near to the receptor. The sensation of sweetness then continues until these localised concentrations become depleted.[6 7] It is now possible to enhance, abolish, or create sweetness by chemical means. Hough has recently reviewed the chemical aspects of sweetness.[8]

Taste dysfunction and disease

Henkin *et al* have listed four major causes of taste (and smell) dysfunction.[9] These are:

Table *Permitted sweeteners[2] in the United Kingdom*

Sweetener	
Intense	*Bulk*
Acesulphame potassium	Hydrogenated glucose syrup
Aspartame	Isomalt
Saccharin	Mannitol
Sodium saccharin	Sorbitol
Calcium saccharin	Sorbitol syrup
Thaumatin	Xylitol

*Aspartame should *not* be used for patients with phenyl ketonuria.

(1) post-influenza hyposmia (diminished sense of smell) and hypogeusia (diminished sense of taste);
(2) idiopathic causes;
(3) head injury;
(4) allergic rhinitis.

Evidently hypogeusia or hyposmia, or both, are much more common in hospital patients (19% of sample tested) than dysgeusia and dysosmia (2%). Environmental or accidental exposure to lead, mercury, or cadmium (or parenteral administration of gold) has been associated with hypogeusia, hyposmia, dysgeusia, or dysosmia. Also decreased concentrations of body metals, particularly zinc and copper, produce severely decreased or disordered taste and smell function. It is therefore not surprising that the copper depleting drug, D-penicillamine, has been associated with the production of hypogeusia. Thiol containing compounds tend to inhibit taste function but several metal ions—for example, zinc, nickel, and copper—tend to restore normal functions. L-Histidine has the same effect. About two thirds of patients with taste and smell dysfunction do not exhibit zinc deficiency but, in those who do, treatment is consistent and takes about two to four months. After treatment with zinc patients usually note that the taste and smell of sweet is the first quality that returns toward normal and bitter is the last. In patients who do not exhibit zinc deficiency cyclic adenosine monophosphate may be involved. It is found that the drug aminophylline improves their hyposmia but not their hypogeusia.

Cancer may affect taste function, and Galili has pointed out that oropharyngeal irradiation produces devastating effects on gustatory perception.[10] Patients with diabetes also show impairment of taste, though this may be specific for some sugars. Thus high thresholds for D-glucose and D-fructose have been reported in adult onset diabetes. This does not seem to affect other basic tastes, and there is apparently no correlation between blood glucose concentrations and taste thresholds. Patients with juvenile onset diabetes display no taste alterations.[10] Patients with renal and hepatic disease may also show taste dysfunction, and sweet nauseation may create a problem in such patients when an essential soluble energy intake is demanded. In these cases glucose syrups[11] constitute a useful alternative to sugar and their hydrogenated forms[12] are of particular value to patients with diabetes.

Conclusions

Sweetness seems to be an inborn pleasurable sensation, but the chemical basis of sweetness is not yet fully understood. Medical observation of taste dysfunction will contribute to our understanding in this respect and, in the meantime, 12 sweeteners are permitted for general use in the UK, in addition to the normal food sugars, which are not regulated. Although many different classes of chemical cause sweetness, there is probably one molecular feature (a 'glycophore') common to them all. Elucidation of the mechanism of taste chemoreception is the goal in this field of endeavour.

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Investigation of urinary tract infection

Urinary tract infection (UTI) is common in infants and children, with a female preponderance except during early infancy. In an early report from University College Hospital, London, Smellie *et al* described 200 consecutively diagnosed children with UTI, of whom 188 were investigated by excretory urography or micturating (voiding) cystourethrography, or both.[1] Abnormalities were found in 50% and in 35% of those investigated after their first infection (47% of boys and 28% of girls). In particular, chronic atrophic pyelonephritis (also known as reflux nephropathy) was detected in 13% of the total; nearly all of these were children with bacteriologically proven or clinically suspected multiple infections. Vesicoureteric reflux was present in 30% of investigated subjects but in 85% of those with pyelonephritis.

Numerous subsequent studies have yielded results in broad agreement with these, the proportion of investigated children showing some radiological abnormality ranging from 25 to 55% and the proportion with reflux from 8 to 52%.[2–9] In at least some of these reports a significant proportion of patients had severe (grade III or IV) reflux in the presence of a normal urogram, suggesting that excretory urography alone is not adequate to exclude serious and potentially damaging reflux.[2 6–9] Since reflux is known to be causally associated with pyelonephritis, which itself is responsible for roughly 20% of the end stage renal failure occurring in European patients below 40 years of age,[10] the early identification of patients with reflux might offer the prospect of preventing some cases of renal failure by appropriate intervention before severe damage has occurred. In addition, some children with UTI have surgically correctable abnormalities of the urinary tract other than reflux, such as obstructive lesions or urolithiasis.

On the basis of arguments such as these, many paediatricians, radiologists, and urologists teach that all children in whom urinary tract infection has been diagnosed should be studied by urography and micturating cystourethrography, the former investigation being necessary to obtain a reliable image of the renal parenchyma, collecting systems, and lower urinary tract and the latter to identify or exclude reflux;[3 7 9] this view seems to be particularly widely held in North America. A few advocate cystoscopy in most or all children,[2 8] but this is certainly a minority opinion. Some experts in the United Kingdom recommend a slightly less invasive approach, in which all children are investigated by urography (or, in appropriately equipped centres, abdominal ultrasonography supplemented when necessary by a renal radionuclide scan), micturating cystourethrography being reserved for children under 5 and patients in whom the urogram is abnormal or who suffer from frequent infections.[11 12]

When experts disagree, how is the non-specialist to decide how to investigate the rather small number of children presenting to him with urinary infection (two a year for the average general practitioner[13])? To answer this question, it is necessary to understand the capabilities and, perhaps more importantly, the limitations of the various techniques available for imaging the urinary tract, so that the most appropriate test or combination of tests can be selected to suit the needs of each particular case.

Excretory urography

Urography is a powerful diagnostic tool that is capable of providing useful information about the entire urinary tract except the urethra. The early (nephrogram) phase shows the renal outlines accurately, particularly when enhanced by tomography, and the slightly later pyelogram phase delineates the pelvicalyceal (collecting) systems. The coarse, irregular scarring of pyelonephritis is readily recognisable, as is the clubbed calyx and overlying cortical thinning of the more localised lesion. Radio-opaque stones will be seen on the control ('scout') film taken before contrast is injected and radiolucent ones show as filling defects. Obstructive lesions such as obstruction of the pelviureteric junction are well shown. In the non-obstructed system renal function can be roughly inferred from the amount of opacified tissue seen on the nephrogram, in the absence of diffuse parenchymal disease such as glomerulonephritis. A reasonably good view of the ureters and bladder (full and empty) can normally be obtained.

Advantages of the method include familiarity, universal availability, and relative ease of interpretation. No other technique approaches it for showing the fine detail of the pelvicalyceal systems. It probably gives a better *overall* view of the renal tract than any other single test. Disadvantages include the risk of allergic reactions to contrast material, which although usually minor can be serious, the discomfort of the injection in small children, the entailed irradiation of the gonads, especially in girls, and the dependence of the image quality on good renal function. Satisfactory pictures are difficult to obtain in infants and especially the newborn. Small renal scars may be missed if located on the anterior or posterior aspect of the kidney.

Micturating (voiding) cystourethrography

Micturating cystourethrography is the definitive method of showing reflux. It also gives a higher definition view of the bladder than excretory urography, and in the lateral projection, during voiding, the urethra is outlined in its full length. Its major disadvantage is the need for bladder catheterisation, which is at best uncomfortable and at worst painful and frightening for small children. Infection may be introduced, and urethral strictures occassionally occur. Nine serious complications of micturating cystourethrography, including two fatalities, were described in a series of 14 children reported by McAlister.[14] As with excretory urography, some gonadal irradiation is inevitable, especially in girls. It is by far the most unpopular procedure with patients and their parents of those considered here.

Ultrasonography

Given up to date equipment and an experienced operator, real time ultrasonography is capable of providing a great deal of information about the anatomy of the renal tract. The shape, size, and position of the kidneys can be determined with considerable accuracy; the degree of 'echogenicity' of the renal substance and the sharpness of corticomedullary differentiation provide a clue to the presence of diffuse parenchymal disease or damage. Hydronephrosis, hydroureter, and ureterocoeles are reliably detected, as are bladder dilatation, trabeculation, and other relatively gross abnormalities of the lower urinary tract. Intermittent dilatation of the retrovesical ureter sometimes provides a clue to the presence of reflux, although normal ultrasonography certainly does not exclude it. Nor does it exclude focal scarring of the kidneys due to pyelonephritis,[15 16] and of course it provides no information at all about renal function. More than any other test mentioned in this annotation, it is 'driver dependent'; at the time of writing, relatively few ultrasonographers have the skill, the experience, or perhaps even the aptitude to obtain the maximum available information from renal ultrasonography, while the pictures themselves are difficult for the clinician to evaluate.

^{99m}Tc dimercaptosuccinic acid (DMSA) scan[17]

DMSA is selectively taken up by renal tubular epithelial cells; the emitted γ radiation can be used to form an 'autoradiograph' of the kidneys, which shows the renal outlines fairly well, though lacking the definition of urography.

Focal scars shows as 'holes' in the image and will be seen even if they are on the anterior or posterior aspect of the kidney, where they are likely to be missed by urography. By counting the radioactivity over the two kidneys, differential renal function can be estimated. The radiation dose is less than urography; reactions to the radionuclide are not seen. The technique gives good results in neonates.

^{99m}Tc diethylenetriamine penta-acetic acid (DTPA) scan

DTPA is handled by the kidney in the same manner as inulin and radiocontrast media such as sodium iothalamate (Conray)—that is, it is filtered at the glomerulus and neither secreted nor reabsorbed by the tubule. When labelled it therefore provides a 'radionuclide urogram' with the same phases as an excretory urogram: nephrogram followed by pyelogram with subsequent visualisation of ureters and bladder. Image definition is considerably inferior to that obtainable by urography, and the technique should not be considered a substitute for it; by measuring the transit time of radioactivity from kidneys to bladder after an injection of furosemide, however, obstructive lesions such as obstruction of the pelviureteric junction can be detected. In a further refinement a secondary rise in activity over one or both kidneys coinciding either with bladder emptying or with a fall in bladder activity without emptying may indicate the presence of reflux.

Purpose of imaging studies

Before submitting a patient to a series of imaging studies of the urinary tract, it is desirable to define as precisely as possible the questions being asked. These will vary according to the age of the patient and the clinical circumstances of the case. They may include any or all of the following:

(i) Is there any structural abnormality of the urinary tract—for example, obstruction, stone, neuropathic bladder—predisposing to infection?

(ii) Are the kidneys scarred as a result of the infection(s)?

(iii) Is reflux present and, if so, in what degree of severity?

Questions (i) and (ii) can be answered with a high degree of reliability either by excretory urography or by a combination of plain abdominal *x* ray, ultrasonography, and DMSA scan. Question (iii) can only be definitively answered by micturating cystourethrography, and it is here that controversy is centred: how important is it to detect every case of reflux after the first infection? Put another way: is it possible to identify subgroups of children in whom the risk of progressive renal damage after their first UTI is so low that cystourethrography can safely be omitted? I believe that with a proper understanding of the epidemiology of chronic atrophic pyelonephritis, it can.

It is difficult to know the exact incidence of UTI in childhood, but a reasonable approximation may be made from a carefully conducted, prospective study published by Dickinson in 1979.[13] He found that 3·1/1000 girls and 1·7/1000 boys, aged 0–14, presented annually with a first, symptomatic UTI; this corresponds to about 780 and 430 per million total population, respectively. (An incidental, but very important, observation made in the same study was that only 18% of children with dysuria and frequency proved to have infected urine, a figure that agrees well with the 24% reported earlier by Williams;[18] this underlines the importance of properly establishing the diagnosis at the first presentation, the single most effective way of avoiding unnecessary investigations.) The incidence of end stage renal failure due to pyelonephritis in Europeans aged <40 is in the region of 4–5 per million.[10] Combining these figures, the crude risk of renal failure due to pyelonephritis in children presenting with a first, symptomatic UTI is not greater than 1% for boys and 0·5% for girls. This must be an overestimate of the true risk as it assumes that detection and investigation of childhood UTI would have identified all those who would later develop renal failure, which is not the case; many adult patients with end stage pyelonephritis have no history of symptomatic UTI in childhood. Furthermore, identification of those with reflux with or without pyelonephritis in childhood would not necessarily lead to prevention of renal failure in all cases. It is therefore likely that the probability that any individual child with a first UTI is at risk from potentially preventable renal failure is of the order of one in several hundred.

The bulk of the published evidence suggests that scarring is present at the first investigation in most of those children in whom renal damage develops.[19 20] A recent study has shown unequivocally that new scars can develop in both previously undamaged and damaged kidneys;[21] as pointed out by Sherwood and Whitaker,[22] however, this is a rare event. In the study of Smellie *et al* new scars were seen in 74 children.[21] In 56 of these, however, 'repeated symptomatic recurrences of infection were recorded'. These cases were assembled from 23 centres over a span of 22 years. Therefore, new scars were seen in only one *asymptomatic* patient per centre every 28 years—hardly a common event.

Suggested scheme of investigation

The following proposed guidelines are similar to, but not identical with, those recently put forward by Whitaker and Sherwood.[23] Three age bands can be identified.

(1) Infants <1 year of age. All cases should be investigated by micturating cystourethrography, ultrasonography, and DMSA scan. If apparatus for or expertise in the last two are not locally available, excretory urography (intravenous urogram) can be substituted, but visualisation of the kidneys and ureters is often unsatisfactory.

(2) Children aged 1–7 years. All children should be studied by either excretory urography or the combination of plain abdominal film, ultrasonography, and DMSA scan.

(3) Children aged 7 years and over. A plain film and ultrasonography are sufficient.

If excretory urography is selected as the initial investigation a strong case can be made for delaying the study for six weeks after the infection has been diagnosed and treated. This is because the characteristic radiological appearances of pyelonephritis are due to contraction of the scar tissue, which replaces the damaged parenchyma, a process that takes time; urography performed immediately after the infection may give a false negative result. In this case a small prophylactic dose of a suitable antimicrobial agent should be continued after the infection has been eradicated until the result of the urogram is known.

A micturating cystourethrogram should be performed in children of 1 year and over if: (i) the infection recurs; (ii) the studies recommended above are abnormal; (iii) the clinical features of the first infection were suggestive of acute pyelonephritis; or (iv) there is a known family history of chronic atrophic pyelonephritis. If this scheme is followed, and provided that the recommended imaging studies are performed and interpreted by staff skilled in the investigation of children, most of those presenting with a first UTI after their first birthday can be spared a micturating cystourethrogram without great risk of missing important reflux.

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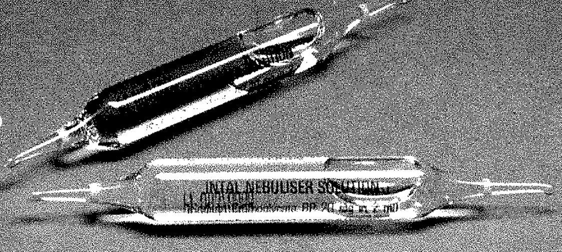

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Original articles

Maternal compared with infant vitamin D supplementation

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SUMMARY Vitamin D metabolites were studied in mother-infant pairs at delivery and eight and 15 weeks after that to evaluate the possibility of vitamin D supplementation of infant through the mother. Healthy mothers (n=49) delivering in January received daily either 2000 IU (group 1), 1000 IU (group 2), or no (group 3) vitamin D. Their infants were exclusively breast fed, and those in group 3 received 400 IU of vitamin D a day. After eight weeks of lactation the infantile vitamin D concentrations were similar in groups 1 and 3 but significantly lower in group 2. The serum 24,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations were also lower in group 2. The mean mineral, parathyroid hormone, and alkaline phosphatase values showed no intergroup differences at any point. No infants showed any clinical or biochemical signs of rickets, and their growth was equal. In conclusion, a daily postpartum maternal supplementation with 2000 IU of vitamin D, but not with 1000 IU, seems to normalise the vitamin D metabolites of breast fed infants in winter. Maternal safety with such supplementation over prolonged periods, however, should be examined.

It has been widely discussed whether breast milk is sufficient to prevent rickets in infants. Several studies have shown that vitamin D supplementation is a necessity for breast fed infants, especially during winter in northern Europe.[1 2] Asian infants in Britain are also at risk of developing rickets.[3 4] Because the poor vitamin D stores of the mother may further impair vitamin D state in the infant,[5] it is important to know whether rickets can be prevented in breast fed infants by supplementation of the mother, especially as some mothers, such as vegetarians, are not willing to give their infants any pharmaceutical medicine.

According to our earlier study, however, normal infant concentrations of vitamin D metabolites could not be reached by giving 1000 IU of vitamin D to the mother.[2] The present study was designed, therefore, to analyse the effects of a larger maternal vitamin D supplementation on the serum vitamin D metabolite concentrations and the mineral metabolism of breast fed infants during winter and spring.

Patients and methods

Study groups. The study was conducted at the maternity wards and outpatient clinic of the department of pediatrics of the University Central Hospital of Tampere (latitude 61°N). Healthy, well nourished mothers delivering in January 1984 were divided in succession into three groups according to vitamin D supplementation as follows:

Group 1: mothers (n=17) given 2000 IU of vitamin D_3 a day, infants not supplemented.
Group 2: mothers (n=16) given 1000 IU of vitamin D_3 a day, infants not supplemented.
Group 3: mothers (n=16) not supplemented, breast fed infants given 400 IU of vitamin D_2 a day.

The serum samples of the mother-infant pairs were collected at delivery and eight and 15 weeks later under exclusive breast feeding, when the infants were also examined. Venous blood samples were collected from the umbilical cord at delivery and within two hours of delivery from the mothers. During pregnancy, 33 mothers had no vitamin D supplementation (group A), eight mothers received 500 IU a day of vitamin D during the second trimester of pregnancy (group B), and eight mothers 500 IU a day throughout the pregnancy (group C). The mothers from these three groups supplemented during pregnancy were distributed into the three groups supplemented after delivery as follows: group 1=11:4:2 (A:B:C, respectively), group 2=9:4:3, and group 3=13:0:3. The mothers received detailed information on the study and gave their written consent.

Sample analysis. The blood samples were collected without anticoagulant and centrifuged immediately after clotting; the serum samples were stored at −70°C until analysed. The vitamin D metabolites 25-hydroxyvitamin D (25-OHD), 24,25-dihydroxyvitamin D (24,25(OH)$_2$D), and 1α,25-dihydroxyvitamin D (1α,25(OH)$_2$D) in all the serum samples (0, 8, and 15 weeks) of each mother-infant pair (2×3) were analysed in the same assay. The other serum variables calcium, albumin, inorganic phosphorus, parathyroid hormone, and alkaline phosphatase were measured after each control—that is, at delivery and eight and 15 weeks thereafter. Heparinised, anaerobic infantile blood samples for ionised calcium were analysed immediately after collection.

Serum vitamin D metabolites were analysed from 1–2 ml samples, to which tritiated vitamin D$_3$ derivatives had been added to monitor recovery. The samples were deproteinised and prepurified, using the acetonitrile-C$_{18}$ Sep-Pak procedure of Turnbull *et al*,[6] followed by further purification and separation of the metabolites by high performance liquid chromatography. A Waters Z-module equipped with a Resolve silicic acid cartridge eluted with hexane-isopropanol-methanol (90–10–1) was used. 25-OHD and 24,25(OH)$_2$D were quantitated by competitive protein binding assay, employing serum from a pregnant woman diluted 1/20 000 in barbital-acetate buffer, pH 8·6, and [^{3}H] 25-OHD. Non-radioactive 25-OHD served as standard. 1α,25(OH)$_2$D was analysed by the radioreceptor assay of Reinhardt *et al*.[7] For the 25-OHD and 24,25(OH)$_2$D assay, the intra-assay (n=10) variation coefficients were 11·6% and 12·5% and the interassay (n=6) variations 10·8% and 14·5%, respectively; for the 1α,25(OH)$_2$D assay the intra-assay variation coefficient was 15·7%, whereas the interassay variation was 11·1%.

Serum calcium concentrations were assayed by atomic absorption spectrophotometry. Plasma ionised calcium and pH were measured by ion selective electrodes (ICA-1 Radiometer A/S, Copenhagen, Denmark). Serum albumin concentration was determined by the bromcresol purple technique, using a Hitachi 705 analyser, inorganic phosphorus by the phosphomolybdate method, serum parathyroid hormone by midregion-(44–68)-specific radioimmunoassay with commercial reagents from Immuno Nuclear Corporation (Stillwater, Minnesota, United States), and alkaline phosphatase activity with a system Olli 3000 analyser with Oriola reagents (Helsinki, Finland), made to correspond to the Scandinavian recommendation.

Statistical analysis. Statistical analysis was performed using two tailed paired *t* test for intragroup differences and Student's *t* test for intergroup differences and for the correlation coefficient.

Results

Serum concentrations of vitamin D metabolites in the mother-infant pairs are presented in Figure 1,

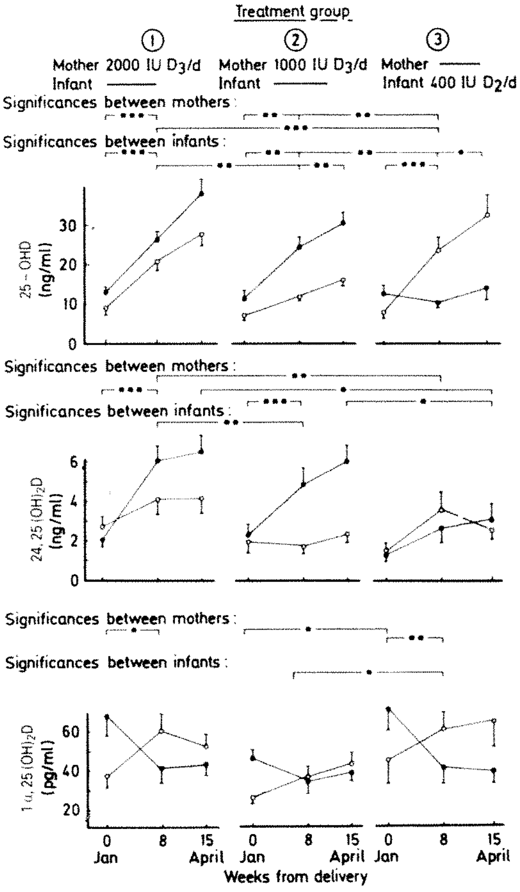

Fig. 1 *Serum vitamin D metabolite concentrations (mean (SEM)) in winter of mothers (●) and infants (○) in different groups with vitamin D supplementation at delivery and 15 weeks later.*

*$p<0·05$, **$p<0·01$, ***$p<0·001$. A detailed table of the concentrations of the vitamin D metabolites can be obtained at request from the author.

Conversions: traditional to SI units – 25-OHD:1 ng/ml=2·5 nmol/l; 24,25(OH)$_2$D:1 ng/ml=2·4 nmol/l; 1α,25(OH)$_2$D:1 pg/ml=2·4 pmol/l.

and the corresponding serum minerals (calcium, ionised calcium, and inorganic phosphorus), albumin, parathyroid hormone, and alkaline phosphatase in Figure 2.

Maternal data. At delivery, the concentrations of 25-OHD (mean (SEM)) were significantly lower (p<0·01) in mothers not receiving vitamin D during pregnancy than in those receiving 500 IU of vitamin D a day throughout pregnancy (10·1 (1·0) ng/ml (25·3 nmol/l), n=31, and 23·0 (4·5) ng/ml, n=8, respectively). Maternal supplementation during middle pregnancy only did not influence the concentrations of 25-OHD (10·7 (1·8) ng/ml, n=8) at delivery. There was a close association between the corresponding 25-OHD concentrations in maternal and cord serum samples (r=0·8023, p<0·001, n=47), but there was no correlation for $24,25(OH)_2D$ (r=0·1725, NS) and only a slight positive correlation for $1\alpha,25(OH)_2D$ (r=0·3328, p<0·025).

As expected, the postpartum maternal vitamin D supplementation increased the serum 25-OHD and $24,25(OH)_2D$ concentrations of mothers significantly (Fig. 1) during the follow up of 15 weeks. During the first eight weeks maternal $1\alpha,25(OH)_2D$ concentrations in all groups decreased to a constant concentration, where they stayed thereafter.

There were no significant intergroup differences in maternal calcium, inorganic phosphorus, albumin, alkaline phosphatase, and parathyroid hormone values (Fig. 2) at any of the study points.

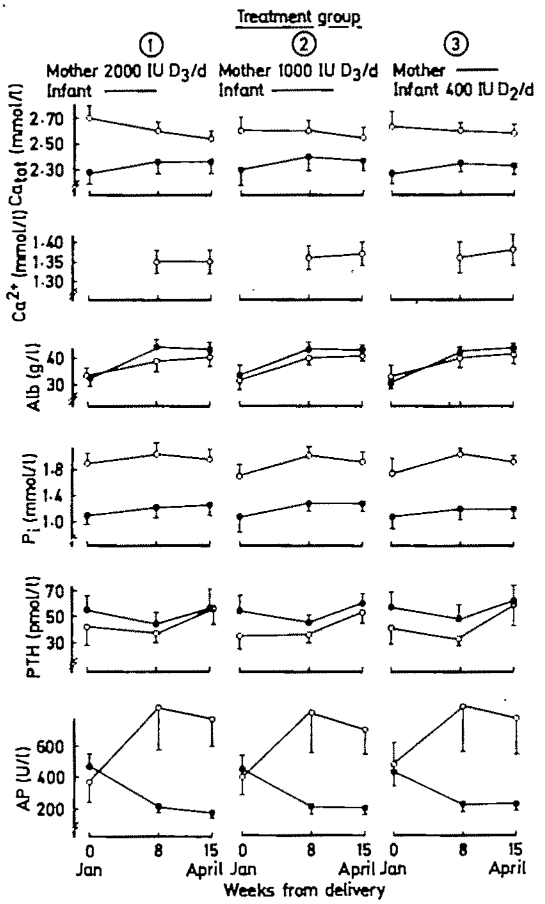

Fig. 2. *Maternal (●) and infantile (○) values (mean (SD)) for serum total calcium (Ca$_{tot}$), ionised calcium (Ca^{2+}), albumin (Alb), inorganic phosphorus (P$_i$), parathyroid hormone (PTH), and alkaline phosphatase activity (AP) in different winter groups with vitamin D supplementation at delivery and eight and 15 weeks later. There were no significant intergroup differences at any study point.*

Infant data. At birth, the serum concentrations of all three vitamin D metabolites were comparable in all groups. The mean (SEM) concentrations of 25-OHD were lower in cord serum samples (8·5(0·9) ng/ml) than in maternal serum samples (11·9(1·1) ng/ml). There was no difference between the umbilical and maternal serum concentrations of $24,25(OH)_2D$ (2·1(0·3) ng/ml (5(0·8) nmol/l) and 1·9(0·3) ng/ml, respectively). The umbilical serum $1\alpha,25(OH)_2D$ concentrations (35(4·4) pg/ml (84 (10·6)pmol/l)) at delivery were 56% of the corresponding maternal concentrations (63(5·5) pg/ml) (p<0·001, n=49).

At 8 weeks of age the 25-OHD concentrations of the infants in groups 1 and 3 were similar, but in group 2 they were significantly lower (p<0·01), and in three infants 25-OHD concentrations were at or below the so called risk limit for rickets (5 ng/ml).[8] In group 2 the $24,25(OH)_2D$ and $1\alpha,25(OH)_2D$ concentrations of infants were significantly (p<0·01) lower than in group 1 and the $1\alpha,25(OH)_2D$ concentrations significantly (p<0·025) lower than in group 3.

At 15 weeks of age, the infant 25-OHD concentrations were significantly (p<0·01) lower in group 2 than in groups 1 and 3, which were similar. The intergroup differences found at 8 weeks of age for $24,25(OH)_2D$ and $1\alpha,25(OH)_2D$ were absent at 15 weeks of age.

The intergroup differences in weight and height between the infants were not significant. At 8 weeks of age, however, two of the three infants in group 2 with low serum 25-OHD concentrations had a low weight gain (500 g and 1160 g) compared with the mean (SD) of the other infants in this group (1540 (383) g).

There were no significant intergroup differences in the infantile serum mineral concentrations (calcium, ionised calcium and inorganic phosphorus), nor in the albumin or parathyroid hormone concentrations and alkaline phosphatase activities (Fig. 2) between the study points, and none of the infants had any clinical signs of rickets.

Discussion

The purpose of the present study was to evaluate the possibility of vitamin D supplementation of infant through the mother. During the last decade, breast feeding has become increasingly popular in many western countries.[9] It has been suggested that nutritional rickets[10] or low 25-OHD concentrations[2,11] are associated with unsupplemented breast feeding. Even intrauterine vitamin D deficiency may give rise to poor growth in infancy unless supplements are given.[12] Prenatal and postnatal vitamin D supplementation is advised for Asian infants living in Britain.[13] Greer *et al*, in a double blind prospective study, have reported decreased bone mineral content of infants receiving breast milk alone,[14] but in a simultaneous larger, but not blind, study Roberts *et al* could not confirm these findings.[15] Another study has suggested that human milk alone may provide sufficient dietary vitamin D for the needs of term infants under optimal social and environmental circumstances.[16] Two of the three above studies[14,15] were performed at moderate latitudes, and all three studies consist of mixed summer-winter populations, while at the latitude of Tampere the amount of sunlight very much depends on the season.[17]

According to the present data, it seems that the milk of supplemented mothers alone may provide the infant with sufficient vitamin D if the dose given to the mother is large enough. When the mother received 2000 IU of vitamin D a day the 25-OHD concentrations of the infants nearly equalled those of the infants receiving 400 IU of vitamin D directly. The dose of 1000 IU of vitamin D daily given to the mother is not high enough, which agrees with the result of our earlier study.[2]

A similar tendency in results, showing a transfer of 25-OHD (or vitamin D) from the mother with 2100 IU, but not with 900 IU of vitamin D daily, to the breast fed infant has recently been described by other Finnish investigators.[18] In this report, however, the season was not controlled. In a Norwegian study the daily dose of 400 IU of vitamin D to mothers during lactation had no apparent effect on the serum 25-OHD concentration of breast fed infants.[11] On the other hand, a double blind South African study showed a clear effect on infant 25-OHD concentrations by even 500 IU of daily vitamin D supplementation through the mother.[19]

In our earlier study the results were similar.[2] The breast fed infant of mothers receiving 1000 IU of vitamin D_2 a day still had, in winter, however, lower 25-OHD concentrations (5·6(3·7) ng/ml) than in the present study ($p<0{\cdot}005$) at the same stage (eight weeks) of lactation, which raises the question whether the vitamins D_2 and D_3 are metabolised differently in man. This has also been suggested in some recent studies.[20,21] The present study used vitamin D_3 instead of vitamin D_2 for technical reasons and was not designed to compare the two forms of vitamin D.

During eight weeks, $1\alpha,25(OH)_2D$ increased in all infant groups to a concentration similar to that described earlier,[22] but the slowest rate of increase was in group 2. As there were no disturbances in the infant mineral metabolism in group 2 (Fig. 2), the $1\alpha,25(OH)_2D$ concentrations can be considered adequate, despite low 25-OHD concentrations in this group. The infantile $24,25(OH)_2D$ concentrations were significantly lower in group 2 than in group 1, which may reflect a reduction in the availability of 25-OHD.

It is unclear whether low 25-OHD concentrations are disadvantageous to growing infants. In 1936 Stearns *et al* reported more rapid growth in infants given 340-400 units of vitamin D daily than in those given 60–135 units.[23] In the present study the differences in infantile supplementation routes did not influence the weight or height gains of an infant up until 15 weeks. The low weight gain in two infants in group 2 may be associated with low 25-OHD concentrations, although this finding cannot be considered significant. It must be remembered that rickets occurs much later than 15 weeks, and normal mineral metabolism and growth at eight and 15 weeks may be of little reassurance.

This study shows once again that the cord blood 25-OHD concentration correlates well with maternal concentrations.[24,25] The concentration of 25-OHD in the maternal circulation seems to be the major factor governing neonatal concentrations. Some of the mothers were supplemented throughout pregnancy with vitamin D, which was clearly reflected in their serum 25-OHD concentrations at term. Their infants also had higher cord serum 25-OHD than those of the unsupplemented mothers. The maternal supplementation during pregnancy did not create any intergroup differences at term as the mothers were evenly distributed among the three groups.

During eight week lactation, maternal $1\alpha,25(OH)_2D$ decreased to normal adult concentrations and remained quite constant thereafter (Fig. 1), which has also been previously shown in man.[26] The normal parathyroid hormone concentrations also confirmed the above results. The rise in maternal 24,25(OH)$_2$D was concomitant with that of 25-OHD (Fig. 1), which has not been reported in an earlier study with a similar supplementation and a long study period.

In conclusion, the vitamin D supplementation of 400 IU/day to breast fed infants is adequate and the most secure way of preventing rickets during winter on northern latitudes. Breast milk does not have enough antirachitic activity by itself or when the mothers are supplemented with 1000 IU/day. A sufficient supply of vitamin D to the breast fed infant is achieved only by increasing the maternal supplementation up to 2000 IU/day. As such a dose is far higher than the daily dietary allowance recommended for lactating mothers[27] its safety over prolonged periods is not known and should be examined.

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Age at diagnosis and abilities in idiopathic hypercalcaemia

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SUMMARY Forty three children aged 6 to 16 years with a documented history of idiopathic infantile hypercalcaemia were assessed on a variety of cognitive and behavioural measures. No relation was found between the age at which hypercalcaemia was diagnosed and subsequent full scale intelligence quotients (IQ) and reading or spelling abilities. Verbal IQ was, however, significantly higher than performance IQ, which had an inverse relation with age at diagnosis. Furthermore, scores for deviant behaviour were found to correlate with age at diagnosis. Thus the characteristic psychological profile of this syndrome may be in part a function of hypercalcaemia during infancy.

Idiopathic infantile hypercalcaemia was first recognised in 1952 by Fanconi *et al*, Lightwood, and Payne.[1-3] Most authors have distinguished 'mild' cases of idiopathic infantile hypercalcaemia,[4] who make a complete recovery, from 'severe' cases,[1] who present in a similar fashion but are characterised by congenital defects and considerable long term morbidity. It is as yet unproven whether the two forms represent differing polarities of the same pathological process or two separate disease entities.[5] The focus in this study is on the severe form of idiopathic infantile hypercalcaemia of the Fanconi type.

Features of the syndrome include a distinctive 'elfin like' facies,[6] renal and cardiovascular abnormalities (supravalvular aortic stenosis and peripheral pulmonary artery stenosis),[5 7] and moderate to severe degrees of mental handicap.[8-10] The children also have a peculiar psychological profile and specific personality characteristics, which seem to distinguish them from other mentally handicapped groups.Their verbal abilities tend to be superior to their visuospatial and motor skills,[9 11] and they show high rates of emotional and behavioural disturbances and hyperactivity.[8 11]

The cause of the syndrome is unknown. Prenatal growth is involved as the birth weights of the affected children are significantly lower than normal, and cardiac murmurs are often noted at birth.[7] Symptoms of hypercalcaemia present during the first year, the peak being between 5 and 8 months of age;[12] but there is often considerable delay between the onset of symptoms and diagnosis. Martin *et al* found the mean age at diagnosis to be 12 months,[7] and the mean time from the stated onset of problems to diagnosis was nine months. The cause of hypercalcaemia may be increased intestinal absorption of calcium. As evidence of excessive vitamin D intake during infancy has not been found,[7] other theories have been proposed, including vitamin D 'sensitivity'.[13] Martin *et al* found normal concentrations of vitamin D metabolites in plasma, however, in both the hypercalcaemic and normocalcaemic phases of the syndrome.[14]

It has been suggested that hypercalcaemia per se may account for the mental handicap seen in the Fanconi type of idiopathic infantile hypercalcaemia and that delay in diagnosis may have a deleterious effect on cognitive development.[5 12] This important question has not previously been studied. In 31 cases where cognitive or developmental assessment results were available a significant negative correlation between age at diagnosis and subsequent intelligence and developmental quotients has been found. (Martin NDT. Personal communication.) These data were, however, retrospective, obtained from hospital records, and based on a range of different tests administered by different testers. Most children were assessed in infancy on the Griffiths scales, but others were assessed when they were of school age on the Wechsler intelligence scale for children or the Stanford-Binet intelligence test. Clearly, different skills and abilities had been assessed at different stages of development on different tests.

The present study examines the relation between age at diagnosis and subsequent cognitive abilities, attainment, and behaviour in 43 mentally handicapped, school aged children with documented evidence of hypercalcaemia in infancy who had been treated with low calcium and vitamin D restricted diets.

Subjects and methods

The children were drawn from the membership of the Infantile Hypercalcaemia Foundation, a parent support group that holds the only register of affected children in the United Kingdom. The parents of 52 children (who had an age range of 6–16 years) known to the Foundation were approached for permission to include their children in the study. Consent was obtained for 49 of the children. Thirty three of these children had been examined by Martin *et al* as part of an earlier study and had been found to fulfil the criteria suggested by these authors for a diagnosis of the Fanconi type idiopathic infantile hypercalcaemia.[7] The hospital records of the remaining 16 children were examined and evidence for a diagnosis of the Fanconi type of idiopathic infantile hypercalcaemia in accordance with these criteria was found in 10 cases. The final sample thus comprised 43 children. Characteristics of the sample and medical data obtained from hospital records are presented in the Table. All the children had been placed on a low calcium and vitamin D restricted diet after diagnosis, for periods ranging from six to 66 months, and a few were still on the diets at the time of the present study.

Each child was seen individually, either at school (34 children) or at home (nine), and assessed on the following measures, without specific knowledge of the age at which the diagnosis had been made:

(1) Intelligence was determined using the Wechsler intelligence scale for children-revised (WISC-R).[15]

(2) Reading and spelling attainment were assessed using the Neale analysis of reading ability[16] and the Vernon graded word spelling test.[17]

Table *Characteristics of the sample studied*

	Mean	*(SD)*
Age (months)	134·5	(36·1)
Age at diagnosis (months)	11·5	(7·8)
Birth weight (kg)	2·7	(0·5)
Plasma calcium at diagnosis (mmol/l)	3·3	(0·4)
Sex (boys:girls)	20:23	

(3) Emotional and behavioural disturbance was determined by the Rutter questionnaires.[18 19] In addition to the total scores on these questionnaires, subscale scores were obtained on symptom clusters of 'neurotic', 'anti-social', and hyperactive behaviours.

Statistical analysis. The Student's *t* test for paired samples was used to compare the subjects' verbal and performance intelligence quotients (IQs), and χ^2 tests were used to compare rates of behavioural disturbance in the present sample with those reported by other researchers for groups of normal and mentally handicapped children. The relation between age at diagnosis and measures of cognitive functioning and behaviour was examined using Pearson product moment correlations.

Results

Cognitive functioning and behaviour. For nine children (21%) full scale IQs on the WISC-R fell below the basal level of 40. The IQs of the remaining 34 children ranged from 40 to 89, with a mean of 54·6. Overall, 54% of the sample fell into the 'severe' range of mental handicap. Only one child had a full scale IQ in the 'borderline' range, and one child came within the 'normal' range. Considering verbal and non-verbal performance IQs separately, eight children (19%) failed to score above the floor of the verbal scale, and for the rest verbal IQs ranged from 45 to 109, with a mean of 62·4. On the performance scale, 14 children (33%) scored below the floor of the test, and the remaining children obtained a mean IQ of 55·9 (range 45–73). There was a significant difference between the scores on these two scales ($p<0·001$), with the verbal scale IQ being superior to the performance scale IQ.

Over half of the subjects attained some score on the Neale analysis of reading ability (22 children) and on the Vernon spelling test (23). The readers had a mean chronological age of 12·0 years (range 72–189 months) and they obtained a mean age of 7·8 years for both reading accuracy (range 74–137 months) and reading comprehension (range 75–144 months). The spellers had a mean chronological age of 12·1 years (range 89–189 months) and obtained a mean spelling age of 6·8 years (range 67–136 months).

Parent and teacher ratings on the Rutter scales indicated high rates of behavioural and emotional disturbance in the sample. Altogether 53% of the children showed disturbed behaviour both at home and at school, and a further 35% were rated as disturbed either at home or school. Only 12% of the sample scored below the cut off for deviant behaviour on both the parent and teacher scales. These rates of disorder are significantly higher than the rates reported by Rutter *et al* for groups of normal children ($p<0\cdot001$) and also mentally handicapped children ($p<0\cdot05$).[19] The children were also found to be significantly more hyperactive on these scales than both normal children ($p<0\cdot001$) and other mentally handicapped children ($p<0\cdot05$),[20] with 72% of the sample displaying hyperactive behaviour either at home or at school or in both settings.

Age at diagnosis and subsequent IQ and behaviour. In view of floor effects on the WISC-R verbal and performance IQs, the relation between cognitive abilities and age at diagnosis was examined using the sums of scaled scores on the WISC-R subtests.

Over the total sample there were no significant correlations between age at diagnosis and the sums of scaled scores on the WISC-R full scale, verbal scale, or performance scale. For the 22 readers and 23 spellers there was also no relation between age at diagnosis and performance on the reading and spelling tests. Examination of scattergrams of the relations among these variables, however, revealed three cases with an extreme score on only one variable, which may have distorted the relations. These three cases comprised the one whose chronological age was by far the highest at diagnosis (47 months), the one with the lowest chronological age at diagnosis (3 months), and the one with the highest IQ score (full scale IQ=89). Excluding these three children from the sample, a negative correlation was obtained between age at diagnosis and the sum of scaled scores on the WISC-R performance scale that was just short of conventional significance ($r=-0\cdot25$, $p=0\cdot06$). This suggests a tendency for children who were diagnosed later to perform more poorly on tasks involving non-verbal visuospatial and motor abilities.

Examining the relation between age at diagnosis and the Rutter scales, there were significant positive correlations with the total behavioural deviance scores on the teacher scale ($r=0\cdot30$, $p=0\cdot027$) and with the hyperactivity subscale scores on both the teacher and parent scales ($r=0\cdot41$, $p=0\cdot004$ and $r=0\cdot28$, $p=0\cdot036$, respectively).

Discussion

Age at diagnosis has been accepted as the best estimate of duration or severity of hypercalcaemia in this condition. Unlike, for example, congenital hypothyroidism, it is not possible to date the onset of hypercalcaemia. Cases have been documented with normal plasma calcium concentrations at birth and in the first few months of life.[21] Hypercalcaemia almost certainly develops at variable times during the first year of life. Moreover, plasma calcium concentrations at diagnosis cannot be equated with severity as rapid rises in plasma calcium concentrations might theoretically precipitate earlier diagnosis. This hypothesis is compatible with the present finding that plasma calcium concentrations were inversely related to age at diagnosis ($r=-0\cdot26$, $p=0\cdot047$), although an alternative explanation for this finding is that it reflects the natural history of hypercalcaemia to resolve over the first few years of life. In either event, recognising its limitations, age at diagnosis seems the best index to study the possible long term effects of idiopathic infantile hypercalcaemia.

In contrast to earlier assumptions,[5 12] we have found no evidence to support the suggestion that earlier diagnosis may alter overall intellectual ability. More detailed analysis of the psychological profile of these children suggests, however, that hypercalcaemia may indeed have long term effects on certain cognitive functions. The peculiar abilities of these children have often been alluded to but until recently had not been comprehensively studied. We have observed, and reported more extensively elsewhere,[11] significantly better verbal scores on the WISC-R than visuospatial and motor skills in these children. Given that later diagnosis of hypercalcaemia is associated with lower scores on the WISC-R performance scale, without a similar effect on verbal scores, it is possible that hypercalcaemia, or a related variable, may have a differential adverse effect on the development of these non-verbal skills.

Behaviour disorders were first noted in this syndrome by Arnold *et al*,[8] and their findings have since been confirmed.[11] The finding that later diagnosis was also associated with more deviant behaviour and hyperactivity later in childhood was unexpected. Effects of ill health and hypercalcaemia can be postulated at several levels — for example, prolonged ill health and feeding problems in infancy would possibly disrupt the development of stable behaviour patterns.

Hypercalcaemia is known to cause psychiatric disturbance in adult life,[22] and there is now some clinical evidence that it can affect certain areas of psychological development. Detailed histological data on brain morphology from cases with this condition are lacking, and to our knowledge there has been no study of brain cell growth in the presence of hypercalcaemia. Although this study requires confirmation and needs to be extended to include cases with the same phenotype but without documented evidence of infantile hypercalcaemia (Williams-Beuren syndrome), there is now some evidence that hypercalcaemia may adversely affect subsequent development and behaviour. Thus although it is fairly rare, it is a condition worthy of note as it is both simple to diagnose and simple to treat.

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The Medium Chain Triglyceride diet and intractable epilepsy

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SUMMARY Fifty children with drug resistant epilepsy were treated with the Medium Chain Triglyceride (MCT) Emulsion diet. Eight achieved complete control of seizures (four without anticonvulsant drugs), and with the addition of anticonvulsants four had seizures reduced in frequency by 90% and 10 by 50–90%. The best results were obtained with astatic myoclonic and absence seizures, but control of seizures was improved in four children with tonic-clonic and three with complex partial seizures. Food given at the same time as MCT helped to reduce side effects, and an extra dose of MCT before bedtime improved control of nocturnal seizures.

Sixty years ago Geyelin found that many patients with epilepsy remained free of seizures while fasting and for several months after return to a normal diet.[1] Wilder in the same year suggested that the ketonaemia induced by fasting was responsible for this effect and proposed that a 'ketogenic diet', high in fat and low in carbohydrate, should be used in the treatment of epilepsy.[2] This was undertaken in children by Peterman[3] and Helmholtz,[4] and the best results seemed to occur in the younger age groups. Livingston reported over a period of 41 years that he had controlled myoclonic epilepsy in 54% of 975 cases using the ketogenic diet.[5] In spite of these good results, however, the traditional ketogenic diet (87% of dietary energy being provided by fat) has been limited by its unpalatability and nutritional inadequacy in young children. It is also difficult to prepare and has not gained wide acceptance.

Recently, there has been a resurgence of interest in ketogenic diets as many children with seizures—for example, tonic-clonic and astatic myoclonic—are not controlled by anticonvulsants used singly or in combination.[6] After reports that medium chain triglyceride (MCT) was more ketogenic than fat Huttenlocher *et al* introduced MCT as an alternative to fat in their ketogenic diet.[7] They showed that a ketogenic diet using MCT to provide 60% of dietary energy was at least as effective as a 3:1 ketogenic diet (75% of energy provided by fat) in producing ketosis and controlling seizures. As less carbohydrate restriction was involved such a diet became easier to prepare, was more palatable, and was less lipogenic. Schwartz *et al* reported success with both the traditional ketogenic diet and the MCT Oil diet and investigated some of its biochemical effects.[8] More recently, because of the increasing expense of a traditional ketogenic diet and the unpalatability of MCT Oil Schwartz *et al* have introduced a combined diet, named the John Radcliffe II diet, which contains smaller volumes of MCT Oil and includes some saturated fat in the form of cream and butter, etc.[9] Some success with both continued seizure control and improved acceptability has been reported with this innovation. In both these series of Schwartz *et al*[8 9] the MCT Oil was incorporated into the diet as an emulsion with skimmed milk.

Several theories have been suggested about the possible mode of action of these diets.

(i) Millichap *et al* reported lowering of the serum pH with the ketogenic diet,[10] but this was not observed by Huttenlocher *et al* with the MCT diet,[7] and no pH reduction was seen in the studies of de Vivo *et al* of long term ketogenic diets.[11]

(ii) Millichap *et al* suggested that negative sodium and potassium balance was a factor,[10] but subsequent studies found no evidence of this.[7 8]

(iii) Dekaban suggested that hyperlipidaemia might have an anticonvulsant effect,[12] but although raised lipids have been found with the ketogenic diet, this was not observed with the MCT diet,[7] and also no changes in cholesterol or high density lipoprotein proportions have been observed with the diet.[8]

(iv) Severe hypoglycaemia has been reported by

Livingston,[13] but this was not observed in other studies.[7 8]

(v) Reduction in serum alanine concentrations have been reported with the ketogenic but not the MCT diet.[8]

(vi) Huttenlocher reported rises of plasma concentrations of the ketone bodies β-hydroxybutyrate and acetoacetate, and his elegant studies suggested the effectiveness of the diet might be related to blood concentrations of these substances.[14] It is interesting to note that during starvation brain metabolism may alter so that ketone bodies can be utilised as an energy source instead of glucose[15] and that acetoacetate has been shown to have an anticonvulsant effect in experimental animals.[16] Huttenlocher showed that ketone concentrations in plasma rose equally with the ketogenic or MCT diets and that this rise was less in older children, in whom the diet seemed less effective.[14]

(vii) Huttenlocher *et al* suggested the possibility of a direct effect of the fatty acids contained in MCT on cerebral excitability.[7]

We initially attempted to treat 25 children with intractable seizures using the MCT Oil diet but were unable to achieve reasonable palatability, and most patients found it unacceptable. One boy aged 14 with drug resistant absence seizures did persevere with the diet and achieved an impressive improvement in seizure control. After this success we wondered if we might be able to increase the acceptability of the diet by using a proprietary MCT Emulsion as the mechanism of action of this diet would be essentially the same as with the MCT Oil diet, whose efficacy has been well documented.[7 8 14 18]

Patients and methods

In this study MCT Emulsion (Liquigen Scientific Hospital Supplies Ltd, Liverpool) was given. Flavouring was added—namely, Nesquik or synthetic butterscotch—to make the MCT Emulsion more palatable, but several children were able to take it without flavouring. Children admitted to the study were suffering from either astatic myoclonic absence, generalised tonic-clonic, or complex partial seizures, which had failed to respond to the appropriate anticonvulsant given as a single agent. Only children who we considered had a good chance of achieving reasonable function at normal or special school were included in the study.

All children were admitted to hospital and anticonvulsants were withdrawn and were reintroduced only if clinically indicated. Daily energy requirement was assessed on an individual basis by the hospital dietitian. An initial starvation period of one to four days was used to induce ketosis, and then the amount of MCT was slowly increased until 60% of the dietary energy requirement was supplied by MCT. All children received daily supplements of vitamins, iron, and calcium (usually Ketovite syrup 5 ml daily, Ketovite/tablet three times a day, Sytron 5 ml three times a day, and Calcium Sandoz one tablet daily). The average time to build up to full diet was 18 days. Once established on full diet children were allowed home and were reviewed after two weeks. If the seizures were not in remission an anticonvulsant was added. Children continued on the diet for at least two years if well tolerated. Where difficulties with compliance occurred some children were admitted to a residential hospital school. Seizure frequency before beginning the diet and once established on full diet was assessed from records of seizures kept in hospital by medical and nursing staff and at home by parents. We graded control according to percentage reduction of seizure frequency after stabilisation on the diet: complete control represented 100%, excellent control 90–100%, good control 50–90%, and poor control <50% reduction of seizure frequency.

Results

Fifty children with seizures resistant to appropriate anticonvulsants have been treated with MCT Emulsion, 18 with astatic myoclonic, 17 with generalised tonic-clonic, six with absence, one with absence and tonic-clonic, and eight with complex partial seizures.

Twenty four children tolerated full diet—namely, 60% MCT—18 tolerated 50–58%, two tolerated 45%, and six were unable to tolerate the diet. Of the 44 children who tolerated the diet, eight achieved complete control of seizures (four without anticonvulsants), four achieved excellent control, and 10 achieved good control. Of the remaining 22 children, 13 had poor control and nine showed no improvement. Of the 22 children with good to complete control, however, three whose control of seizures was excellent refused to continue the diet. Fifteen children have been on the diet for two years or more and seven for more than a year. Sixteen children remain on the diet, eight with astatic myoclonic, three with absence, three with generalised tonic-clonic, and two with complex partial seizures. Four children, two with astatic myoclonic and two with absence seizures, have been off the diet nine months or longer without recurrence of seizures.

Of the 17 children over the age of 10, one achieved complete, three excellent, seven good, and four poor control of seizures and two were unable to tolerate the diet. Success was often associated with a high level of patient motivation. A boy aged 10 opted to try the diet as an alternative to temporal lobotomy and achieved good control, and a girl aged 11 who had developed anorexia nervosa on MCT Oil was determined to try MCT Emulsion and achieved excellent control of her absence seizures but required the addition of an anticonvulsant (ethosuximide) to achieve complete control.

In addition, 11 children had considerable difficulties with compliance because they would not take the diet or their parents would not administer it properly, despite the fact that five of them had achieved good control or better. Admission to a residential hospital school was accepted by nine of them, and eight achieved good to complete control.

The timing of seizures was of interest: eight children whose seizures had been diurnal before treatment with the diet had seizures only at night on full diet. These nocturnal seizures ceased when an extra bolus of MCT was given at 2000 to 2100h, but it was noted that diarrhoea and abdominal pain occurred if extra MCT was not given with food—for example, biscuits.

Results of different seizure types.

Astatic myoclonic

All 18 of the children in this group (who were aged 2–8 years, with a mean of 4 years) had been tried on sodium valproate, nitrazepam, and clonazepam without reduction of seizure frequency. The results of treatment on MCT diet alone or with sodium valproate or nitrazepam are shown in the Table.

Absence

All of the six children with 'pure absence' seizures and the child with absence and generalised tonic-clonic seizures (who were aged 5–11 years, with a mean of 8 years) had been tried on sodium valproate, ethosuximide, methsuximide, and acetazolamide without reduction of seizure frequency. The child with tonic-clonic seizures had also been tried unsuccessfully on carbamazepine and phenytoin. The results of treatment on MCT diet plus sodium valproate or ethosuximide are shown in the Table.

Generalised tonic clonic

All of the 17 children in this group (who were aged 5–15 years, with a mean of 10 years) had been tried on carbamazepine, phenytoin, primidone, sodium valproate, and each combined with acetazolamide without reduction of seizure frequency. The results of treatment on MCT diet plus an anticonvulsant are shown in the Table.

Complex partial

All of the eight children in this group (who were aged 9–14 years, with a mean of 10 years) had been tried on carbamazepine, phenytoin, primidone, sodium valproate, and each combined with acetazolamide without reduction of seizure frequency. The results of treatment on MCT diet plus carbamazepine or phenytoin are shown in the Table.

Side effects. Mild diarrhoea and abdominal pain were common and were usually alleviated by a temporary reduction of MCT dosage or when MCT was taken in small amounts with food. Side effects led three children, however, who had had excellent control to give up the diet, two of whom have restarted the diet with excellent control.

In 13 children a subjective improvement in mental awareness was observed by parents and nursing and school staff.

One boy aged 10 with severe astatic myoclonic seizures of three years' duration showed a good initial response to the MCT Emulsion diet but later refused to take it. The diet was given by nasogastric tube, but we omitted to give him vitamins through the tube and four weeks later he became blind. His sight was restored four weeks after starting treatment with vitamins.

Table *Control of the different types of seizure on the MCT diet in 50 children with drug resistant epilepsy*

Type of seizure	*No of children*	*Control*				
		Complete (100%)	*Excellent (90–100%)*	*Good (50–90%)*	*Poor (50%)*	*Failed*
Astatic myoclonic	18	3	1	5	5	4
Petit mal	7	3	2	1	1	—
Tonic-clonic	17	1	1	2	7	6
Complex partial	8	1	—	2	—	5
Total	50	8	4	10	13	15

Discussion

These results suggest as previously reported[7 8 17] that the MCT diet is worth considering for children with drug resistant seizures and that using a proprietary MCT Emulsion may improve acceptability.

In contrast to previous studies[8 9] we withdrew anticonvulsants before introducing the diet. We believe it makes no sense to continue to dispense anticonvulsant treatment that is ineffective, but we insist that withdrawal takes place in hospital. The fact that four children with astatic myoclonic seizures managed better on MCT diet off drugs we think justified this approach and also gives credence to the view that the MCT diet contains 'agents' that have anticonvulsant properties. In addition, we have treated older children with a variety of seizures with some success, and this suggests that the MCT diet should be considered in any child of reasonable intelligence suffering drug resistant seizures rather than reserving it for the younger child as has been suggested.[14]

Side effects remain a problem, and we have found that the probable osmotic effects of the diet may be alleviated by giving MCT in regular small amounts with food.

Bilateral optic neuropathy has been reported in two children aged 5–7 who were maintained on a 4:1 ketogenic diet without vitamin B supplements.[19] Blindness occurred 10 months and one year, respectively, after introduction of the diet. Vitamin B supplements and thiamine restored vision in six and 11 weeks, respectively. Our own experience emphasises the importance of giving adequate vitamin B supplements while taking MCT Emulsion.

The reduction of nocturnal seizures afforded by extra MCT at night may relate to the paradoxically low morning concentrations of ketones in children on the MCT diet that have been reported previously.[8 18] Our biochemical observations, reported elsewhere, shed some light on the reasons for this.[20]

It is difficult to compare the results of treatment of our 50 children with the 54 treated by Schwartz *et al*[9] because different seizure types were treated—namely, infantile spasms and partial seizures—and the duration of treatment was not specified, whereas we have attempted to assess control of seizures over the whole duration of treatment, with 22 out of 44 children having received treatment for at least a year at the time of assessment. In their series of 25 children with 'drop seizures', however, 85% had >50% reduction in seizure frequency, whereas in our series of 18 children with astatic myoclonic seizures 50% had >50% reduction in seizure frequency. They provided no information on the eight children they treated with absence seizures, and it is unclear which of the three diets suited the individual children best.

We realise that much of our data on seizure frequency relies on second hand information, but it is difficult to improve on this without either long periods of admission to hospital or prolonged electrical recordings. More reliable records were obtained when nine children were admitted to a residential hospital school for long periods, where teachers and nurses recorded all seizures and the degree of control consequent on this—that is, four complete control, two excellent control, two good control and one would not comply. Two of the children who obtained complete control for six months and then refused the diet did not relapse for three to six months after the diet was withdrawn.

It is our routine to continue the diet and if necessary anticonvulsants for two years after the last seizure. The anticonvulsant is withdrawn slowly and two months later the diet is stopped.

When we see a child with numerous astatic myoclonic seizures in a padded bed for his own protection, drooling, unable to speak or feed himself, and in two weeks on 48% MCT running around the ward, remaining free of seizures for two years and now off treatment for a year without seizures, we begin to ask ourselves if MCT Emulsion should be the first choice treatment for this type of seizure.

We thank the nursing and dietetic staff of the paediatric units at the General Infirmary and St James's University Hospital, Leeds, for their unfailing efforts, Mrs J Crossley and Miss H Shelton for secretarial help, and the nursing staff and teachers at Wharfedale Children's Hospital for their help with these 'difficult' children.

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Twenty five years ago

Disorders of spoken language in young children

Mary D Sheridan (London)—Arch Dis Child 1961;**36**:11–16

'The normal acquisition in early childhood of all the biologically determined skills depends upon timely opportunity to explore, experiment with and learn to understand the world about him, and to realize how he relates to other people. If, through congenital disability or environmental deprivation, the normal methods of learning and communication are not available to him, he must substitute whatever means are open to him, or fail to develop his personality and his intellect. This biological learning appears to reach its zenith in the first two or three years of life and gradually tapers off by the age of 6 or 7 years, after which habits of functioning appear to be firmly fixed.'

Dr Sheridan classifies and discusses the reasons for delay or failure in the development of spoken language under the following headings: impaired hearing; low intelligence; delayed maturation of the central nervous system; brain injury; psychogenic disorders; motor dysfunctions; lesions of the peripheral speech organs.

'The commonest causes of delay in the development of spoken language are deafness and mental backwardness. Regarding the rarer causes of delay it needs to be remembered that lesions of the central nervous system occurring in the first few years of life have been inflicted on plastic and rapidly growing tissues, and only time can tell whether the resulting damage is permanent, or capable of compensation, or open to recovery. The first five or six years are therefore critical for diagnosis, treatment and training.'

(Those who were privileged to know Mary Sheridan quickly realised that they were in the presence of an exceptional person, in spite of her oft repeated protestations that she was only a simple school medical officer reluctantly presenting her findings to the experts. She was a true pioneer and her methods of assessment, particularly in the auditory and visual fields, have stood the test of time. There can be few people whose researches have contributed more to the assessment and care of the handicapped child . . . . NEIL GORDON.)

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Role of octanoic and decanoic acids in the control of seizures

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SUMMARY Octanoic and decanoic acid, the major constituents of the Medium Chain Triglyceride (MCT) Emulsion diet, have been detected in appreciable quantities in the peripheral blood of children with intractable seizures treated with the MCT diet. Serum concentrations of these acids as well as β hydroxybutyrate and acetoacetate rose as the diet was introduced and on full diet showed pronounced diurnal variation and low concentrations in the morning. No correlation between octanoic and decanoic acid concentrations and control of seizures was established, but further studies with octanoic and decanoic acid using animal models are necessary to assess the role of these acids and of control of seizures.

In a recent review Kupferberg reported that experimental animals were afforded optimal protection against seizures induced by pentylenetrazol by C_8–C_{10} carboxylic acids.[1]

The Medium Chain Triglyceride (MCT) diet is a form of neutral lipid triglyceride containing fatty acid molecules with a carbon chain length of 6 to 12, the major constituents being octanoic acid 81% and decanoic acid 15% (Table 1). These acids are lipid soluble and are absorbed rapidly from the gastrointestinal tract through the portal circulation to the liver, where it was assumed that they were metabolised to carbon dioxide, ketone bodies, and long chain fatty acids with little escape into the systemic circulation. Linscheer *et al* were able, however, to measure octanoic acid concentrations in the blood of normal patients and patients with cirrhosis after duodenal infusions and were surprised to find small amounts in the blood of the normal group.[2] From their data we have calculated the mean serum concentration to be about 6 μg/ml.

Recently, we reported significant concentrations of both octanoic and decanoic acids in the serum of children receiving MCT Emulsion for the control of drug resistant seizures.[3]

Table 1 *Constituents of the liquidised MCT diet*

Acid	%
Hexanoic (C_6)	1·1
Octanoic (C_8)	81·1
Decanoic (C_{10})	15·7
Dodecanoic (C_{12})	2·1

It seems reasonable to suggest that as these fatty acids occur in appreciable amounts in the peripheral blood, especially octanoic acid, they could have an effect on the central nervous system. It is known that a direct isomer of octanoic acid—namely, valproic acid—has anticonvulsant properties. The results of our recent study of children receiving the MCT Emulsion diet has shown that four children with drug resistant seizures have remained free of seizures for six months to two years on diet alone.[4] This suggested that the diet contained agents that acted directly or indirectly on the control of seizures. We thought it worth while to investigate the role of octanoic, decanoic, β hydroxybutyrate, acetoacetate, and alanine fatty acids in children taking the MCT Emulsion diet.

Patients and methods

Octanoic and decanoic acids were assayed by gas liquid chromatography as previously described.[3] Blood samples were collected in heparinised tubes and the separated plasma stored at 4°C. All samples were analysed blind in Detroit without the analyst being aware of individual clinical details. Initially, random morning samples were obtained before beginning treatment, during initial starvation, and on full diet. More recently we assayed concentrations at fixed times during a 24 hour period in children who were receiving 50–60% of their energy requirements from MCT Emulsion: (i) at four sampling times in eight children and (ii) at five sampling times in a further nine children. In these children we estimated serum concentrations of β hydroxybutyrate, acetoacetate, and alanine. Two children were included in both studies and a child in the second study had an extra sample taken at 0400h.

Results

The initial morning samples produced undetectable concentrations of octanoic and decanoic acids in five children before treatment and during fasting and in two children after withdrawal of treatment. In children on the MCT Emulsion diet fatty acid concentrations seemed to rise as the amount was increased until 60% of the energy requirements was supplied by the diet (Figs. 1 and 2). Concentrations of octanoic acid were higher than those of decanoic acid. The concentrations obtained compared with blood concentrations for other anticonvulsants—for example, sodium valproate and clonazepam. As there was a wide scatter of results on 'full diet' we decided to sample at fixed times during the 24 hours.

The first study of 24 hour profiles in eight children at 0800, 1200, 1600, and 2000h showed a pronounced diurnal variation of concentrations of octanoic and decanoic acids on 50–60% MCT (Fig. 3). In the second study of 24 hour profiles in nine children at five sampling times—namely, 1200, 1600, 2000, 2400, and 0800h the next day—when the mean values for octanoic and decanoic acids were plotted the same trend was repeated (Fig. 4). A similar diurnal variation was seen with concentrations of β hydroxybutyrate and acetoacetate but not with alanine (Fig. 4).

In one patient the 24 hour profiles at six sampling times—namely, 1200, 1600, 2000, 2400, 0400, and 0800h the next day—showed that the most rapid fall in octanoic and decanoic acids, β hydroxybutyrate, and acetoacetate occurred between 0400 and 0800h (Fig. 5).

Clinical details for the children involved in these

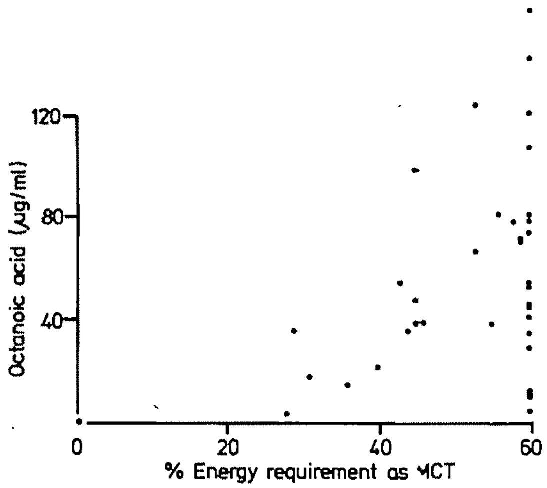

Fig. 1 *Relation between serum concentrations of octanoic acid and increasing amounts of MCT diet.*

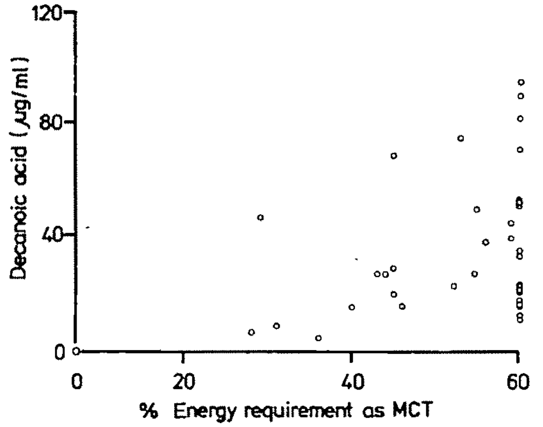

Fig. 2 *Relation between serum concentrations of decanoic acid and increasing amounts of MCT diet.*

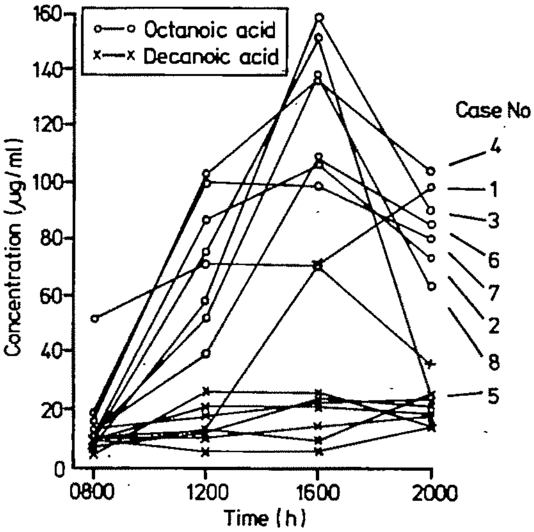

Fig. 3 *Twenty four hour serum profiles of concentrations of octanoic and decanoic acids in eight children at four sampling times.*

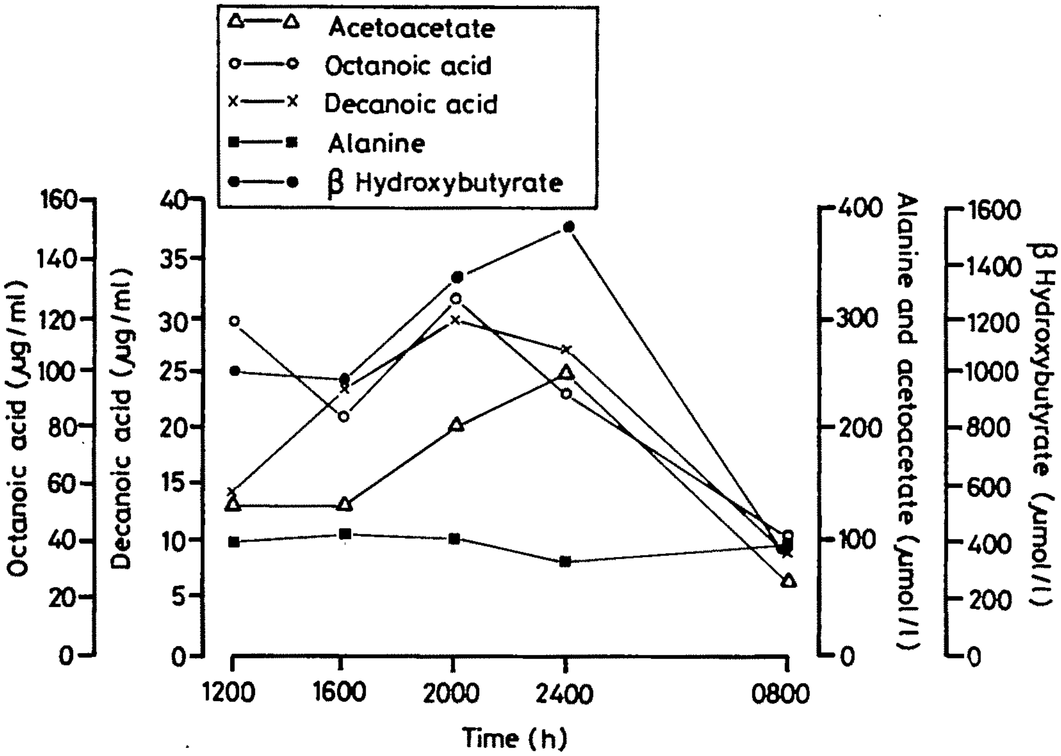

Fig. 4 *Mean serum concentrations of octanoic and decanoic acids, β hydroxybutyrate, acetoacetate, and alanine in nine children at five sampling times.*

two profile studies as regards age at time of study, duration of time since beginning the MCT Emulsion diet, seizure type, and effectiveness of control are shown in Tables 2 and 3 along with the maximum serum concentrations of octanoic and decanoic acids for each child during each profile. Effectiveness of control is assessed according to our reported results.[4]

Discussion

In our initial studies where serum samples were taken at unstandardised times we found the concentrations of octanoic and decanoic acids to vary widely, but a gradual increase in concentrations while becoming established on the diet was suggested. We considered poor compliance a probable cause but wished to check if concentrations fluctuated during the day. We were surprised to find such a wide fluctuation in concentrations in the first profile series, with low morning and high afternoon and evening concentrations common to all patients even after long periods on the diet. This diurnal variation would suggest that octanoic and decanoic acids in MCT are cleared from the blood and presumably metabolised very quickly, indicating that continuous or frequent administration of small doses of MCT would lead to more persistent concentrations, and this might be reflected in a similar change for β hydroxybutyrate and acetoacetate, as our second profile series shows a similar diurnal variation for these ketogenic acids.

Although a relation between control of seizures and β hydroxybutyrate concentrations has been suggested previously, we did not achieve the same high concentrations as Huttenlocher, but we had success in reducing seizures.[5] It may be that optimal control of seizures with MCT Emulsion could be achieved with random β hydroxybutyrate concentrations lower than those suggested by Huttenlocher.[5]

The low morning concentrations were of interest, and we note that low morning ketone concentrations have been reported in children on the ketogenic diet and that this was the opposite to what was seen in normal children.[6 7] The low concentrations might relate to our previous observation that nocturnal seizures were not so readily suppressed on the diet.[4] It is possible that these observations tell us how the diet should be used rather than how it works. MCT Emulsion given at night should improve morning fatty acid concentrations and could reduce the tendency to seizures at the time.

The 15 children involved in these profiles (Tables 2 and 3) had a varied degree of control of seizures and varied types of seizures. It is thus difficult to draw conclusions about the relation between control of seizures and serum concentrations, but all children have optimum concentrations of octanoic acid in excess of 90 μg/ml and maximum concentrations of decanoic acid in excess of 8 μg/ml. There was no clear association, however, between concentrations of these acids and control of seizures, seizure type, age of child, or duration on diet in this small series. A similar lack of correlation between serum concentrations and control of seizures has been found with sodium valproate and clonazepam.

We have therefore not been able to show any definite relation between fatty acid concentrations and control of seizures, but it would not be unreasonable to suppose that octanoic and decanoic

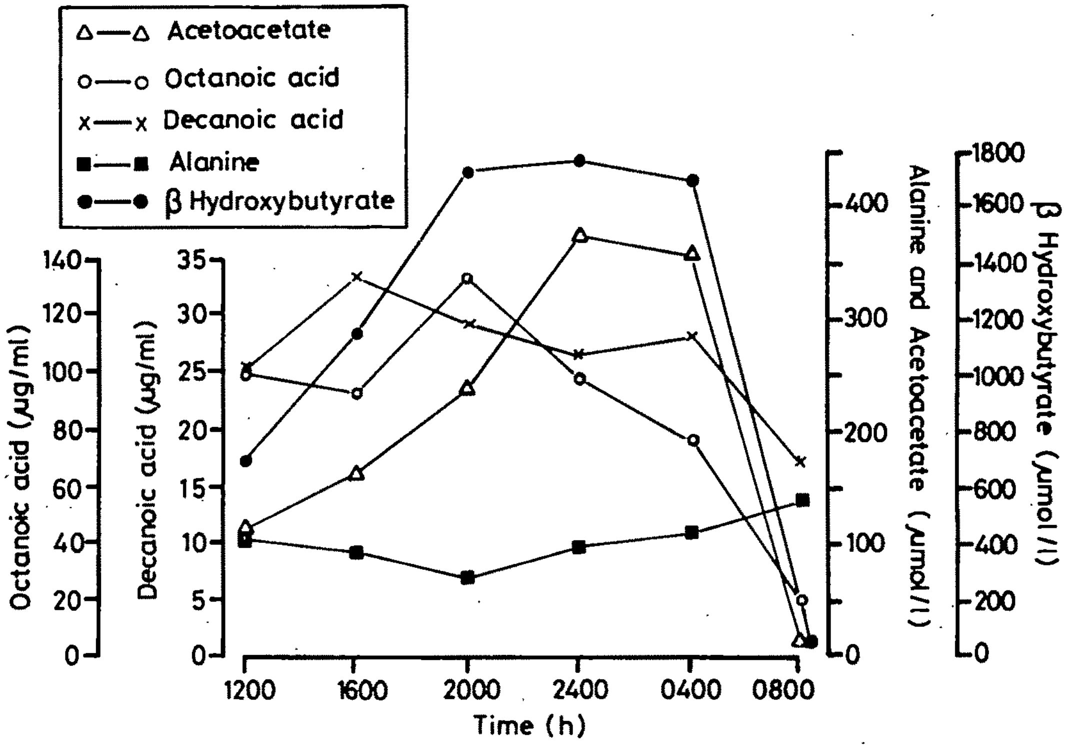

Fig. 5 *Twenty four hour serum profiles of concentrations of octanoic and decanoic acids, β hydroxybutyrate, acetoacetate, and alanine in a patient on full MCT diet at six sampling times.*

Table 2 *Clinical information for the eight patients in Figure 3*

Case no	*Age (years)*	*Diagnosis*	*Seizure control*	*Maximum concentration (μg/ml)*	
				Octanoic acid	*Decanoic acid*
1	9	Grand mal	Good	98·2	12·2
2	3	Astatic myoclonic	Complete	104·7	24·5
3	10	Grand mal	Good	157·7	22·6
4	5	Astatic myoclonic	Complete	134·9	22·4
5	4	Astatic myoclonic	Excellent	149·4	26·6
6	11	Petit mal	Excellent	109·5	15·8
7	13	Temporal lobe	Good	101·7	20·6
8	13	Petit mal	Excellent	137·7	70·1

Seizure control: Complete=100% reduction in seizures; Excellent=90–100% reduction; Good=50–90% reduction; and Poor=<50% reduction.

Table 3 *Biochemical data for the nine children in Figure 4*

Case no	*Age (years)*	*Diagnosis*	*Seizure control*	*Maximum concentration (µg/ml)*	
				Octanoic acid	*Decanoic acid*
1	12	Grand mal	Good	136·2	34·4
2	2	Temporal lobe	Complete	124·0	29·4
3	7	Temporal lobe	Poor	151·0	33·6
4	14	Grand mal	Good	123·3	8·0
5	11	Petit mal	Excellent	123·5	15·2
6	10	Grand mal	Good	175·1	35·5
7	5	Astatic myoclonic	Complete	258·9	80·6
8	13	Astatic myoclonic	Excellent	100·6	23·2
9	8	Temporal lobe	Poor	Samples mislaid*	

Seizure control: Complete=100% reduction in seizures; Excellent=90–100% reduction; Good=50–90% reduction; and Poor=<50% reduction.
*Results for acetoacetate, alanine, and β hydroxybutyrate are available for this patient, however, and are included in Figure 4.

acids could have some influence on seizure discharge, and we think this justifies further investigation.

Conclusions

Our biochemical investigations led us to the following conclusions.

(1) Octanoic and decanoic acids occur in the peripheral blood in appreciable amounts in children receiving MCT Emulsion and are therefore not fully metabolised in the liver.

(2) There was a definite trend for concentrations of octanoic and decanoic acids to rise with an increasing amount of MCT Emulsion.

(3) The concentrations of these acids vary widely during the day and fall rapidly after the last evening dose of MCT, suggesting a short half life.

(4) Similar diurnal variations of β hydroxybutyrate and acetoacetate were seen and these may follow rather than precede the changes in octanoic and decanoic acids.

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Effect of tracheobronchial suction on respiratory resistance in intubated preterm babies

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SUMMARY Measurements of the resistance, time constant, and compliance of the respiratory system were made in 25 mechanically ventilated, preterm babies on 32 occasions, using the single breath technique. Patients were classified according to the level of respiratory resistance by reference to a population of 36 babies studied over the first two days of life before airway secretions had become apparent. There was a highly significant fall in both the resistance and time constant measurements after tracheobronchial suction or lavage for infants whose pretreatment values of resistance were greater than the reference mean. When tracheobronchial toilet was effective in removing secretions the changes in resistance and time constant values were again significant. No changes in compliance values were noted. Severe but clinically inapparent mucous obstruction of the airways was revealed in two infants by a progressively rising respiratory system resistance during continuous monitoring. The need for and efficacy of tracheobronchial suction and lavage could be determined by such techniques for monitoring the resistance of the respiratory system during mechanical ventilation.

Routine tracheobronchial suction and lavage are carried out during mechanical ventilation in many neonatal intensive care units. Neither the indications for beginning these procedures nor their optimal frequency has been established. There is now growing evidence to suggest that the adverse side effects of suction or lavage, such as transient bacteraemia,[1] increased intracranial pressure,[2] diminished mucociliary transport,[3] and airway inflammation,[4] may be considerable. In addition, there exists the obvious disturbance to ventilation during the procedure.

In the extreme situation where the airway is almost totally occluded by mucus endotracheal suction produces obvious and rapid clinical benefit. Lesser degrees of mucous obstruction are, however, notoriously difficult to identify in the usual clinical setting. Moreover, using existing techniques, the beneficial effects of chest physiotherapy and suction have been difficult to establish.[5 6]

We therefore set out to try and predict the optimal timing and mechanical benefits of tracheobronchial suction or lavage, by using single breath measurements of lung mechanics[7] to measure the compliance, resistance, and time constant of the respiratory system before and after tracheobronchial toilet in infants with and without clinically obvious airways secretions.

Patients and methods

Patients. To establish a reference range of values of resistance of the respiratory system in intubated, mechanically ventilated, preterm babies 36 babies were studied towards the end of day one of life and 21 babies on day 2 of life. Data collected on days 1 and 2 of life were used because at this stage there was no evidence of appreciable secretions. Mean (SD) gestational age was 29·5 (3·6) weeks and mean (SD) birth weight 1370 (740) g. The babies were divided into two clinical groups:

(1) 25 babies with presumed hyaline membrane disease defined clinically and radiologically;

(2) 11 babies ventilated for non-respiratory or non-cardiac problems who had no clinical or radiological evidence of respiratory disease.

The study group consisted of 25 babies of mean (SD) gestational age 30·6 (4·9) weeks and mean (SD) birth weight 1440 (700) g. They were studied on 32 occasions after the second day of life. All these babies were receiving routine ventilator care, including regular tracheobronchial suction. Some in whom there was a particular clinical indication—that is, large amounts of secretions—were being given additional bronchial lavage. The tests were timed to coincide with routine suction or lavage procedures.

Lung mechanics. All babies had been intubated with a 2·5–3·5 Coles tube (Portex) and ventilated with a pressure limited time cycled ventilator (Vickers Neovent or SLE Newborn). The rate of ventilation was increased until spontaneous respiratory effort was abolished as judged by a uniform run of inspiratory and expiratory volume plateaux in response to the ventilator pressure plateaux. Endotracheal tube gas flow was measured using a double pneumotachograph system[8] linear to at least 12 l/min placed in the bias flow pathway on either side of the infant's endotracheal tube. The pneumotachographs and their transducers (Validyne MP45) were carefully balanced electronically so that the difference between the signals was zero with no flow through the endoctracheal tube. The difference signal during a measurement was thus the baby's tidal flow.

Airway opening pressure was measured at the oral end of the endotracheal tube using an SE Labs 1150 pressure transducer. Flow and pressure signals were fed through an Emma 4001 amplifier system and recorded simultaneously on a UV chart recorder (SE Labs) and after digitisation at 100 Hz per channel on a microcomputer (Apple II). Flow was passively integrated to give a volume signal on the chart recorder and digitally integrated by microcomputer.

Recordings were taken of airway opening pressure and flow during mechanical ventilation for at least two periods of 30 seconds at 10 minute intervals. The flow and volume signals were displayed on the visual display unit of the microcomputer and the values of flow and volume between 50% and 97% of the total expired volume were submitted to linear regression analysis to obtain the slope of the flow-volume relation, which is equivalent to the time constant of the respiratory system under passive conditions.[7] Compliance of the respiratory system was the ratio of the expired tidal volume, corrected if necessary for incomplete expiration,[9] to the measured peak to end expiratory difference in airway opening pressure.

From the values of compliance (C_{rs}) and time constant (T_{rs}), resistance (R_{rs}) was calculated as follows:

$$T_{rs}=C_{rs}\times R_{rs};\ R_{rs}=T_{rs}/C_{rs}$$

Mean values of time constant, compliance, and resistance were derived from analysis of between three and 12 breaths from each 30 second sample. Mean coefficients of variation of compliance, resistance, and time constant by our technique are 2·3%, 5·7%, and 5·7%, respectively.[8]

We did not subtract the endotracheal tube resistance from the measured respiratory system resistance as functionally the endotracheal tube forms part of the infant's airway.

Endotracheal tube suction and lavage. Suction was carried out using a size 6 FG catheter with side hole and end holes (Portex), which was introduced through the endotracheal tube, passed as far as easily possible, and then withdrawn by 0·5 cm. Suction was then applied during withdrawal using negative pressures no more than 40 cmH_2O. If secretions were noted in the catheter the procedure was repeated once. The baby was then reconnected to the ventilator and after a period of five minutes at the pre-existing settings the measurements of lung mechanics were repeated.

In the lavage group the same procedure was followed after introducing 0·5 ml normal saline down the endotracheal tube, reconnecting the baby to the ventilator for five breaths, and then following the suction procedure described above except that in this group the procedure was always repeated at least once.

Most measurements were made before and after routine suction or lavage. Occasionally, during the course of a study, values of resistance, which were being continuously updated by computer analysis, were found to be progressively increasing. Appropriate action was taken and in two cases the individual data are described in detail.

Analysis. As the reference values of resistance, compliance, and time constant of the respiratory system on the first two days of life were shown to have a log normal distribution all analysis was performed after logarithmic transformation. Paired *t* tests were used to compare the before and after suction or lavage. Data from infants with or without obvious secretions were analysed separately.

Results

In the reference population there was little difference between the mean values of respiratory system resistance of babies with hyaline membrane disease or without respiratory disease on either the first or second days of life. Overall, the combined data gave a mean value of resistance of 195 $cmH_2O/l/sec$ (confidence limits 66–562 $cmH_2O/l/sec$) for the reference group of intubated babies during the first two days of life.

When the study group was classified according to the pretreatment value of resistance there were striking differences in the effect of endotracheal tube suction and lavage on respiratory system mechanics (Table 1). If the initial resistance was greater than the mean reference value for days one and two of life (Table 1 group D) there was a highly significant drop in resistance and time constant values after suction or lavage, whereas compliance values were unaltered. The changes in resistance were most striking for those groups of infants whose pretreatment resistance was highest (Table 1 groups A and B). When the pretreatment resistance values were less than the mean reference values, however, there was no measurable benefit from suction or lavage. The group as a whole had a highly significant decrease in resistance and time constant after tracheobronchial suction or lavage but no change in compliance (Table 1).

There were pronounced differences in the effect of suction or lavage on lung mechanics, according to whether or not the procedures were effective in removing airway secretions (Table 2, Fig. 1). Simple endotracheal tube suction had a just significant effect on resistance and time constant when obvious secretions were obtained. When secretions were obtained by bronchial lavage on the other hand resistance fell markedly along with time constant. After ineffective bronchial lavage there was a

Table 1 *Effects of endotracheal suction or lavage according to pretreatment total respiratory resistance. Values are mean (95% confidence limits) for pre- and post-treatment*

Group	*Pretreatment respiratory resistance*	*n*	*Respiratory system*					
			Resistance ($cmH_2O/l/sec$)		*Time constant (sec)*		*Compliance (ml/cmH_2O)*	
			Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*
A	More than 2SD above reference mean	4	691 (610,783)	352 (181,684)*	0·30 (0·16,0·54)	0·18 (0·12,0·26)	0·52 (0·23,1·17)	0·53 (0·39,0·72)
B	Between 1 and 2SD above reference mean	4	394 (310,498)	263 (201,343)*	0·22 (0·09,0·51)	0·09 (0·04,0·20)**	0·44 (0·27,0·74)	0·37 (0·17,0·78)
C	Up to 1SD above reference mean	9	251 (201,313)	224 (170,295)*	0·16 (0·06,0·44)	0·14 (0·07,0·30)	0·63 (0·22,1·76)	0·64 (0·28,1.43)
D	All patients greater than reference mean	17	355 (153,824)	257 (149,445)**	0·20 (0·07,0·25)	0·14 (0·06,0·31)**	0·55 (0·22,1.46)	0·54 (0·23,1·24)
E	All patients less than reference mean	15	120 (37,393)	137 (73,257)	0·11 (0·03,0·45)	0·09 (0·02,0·32)	0·68 (0·17,2·74)	0·67 (0·16,2·71)
F	All patients	32	224 (67,745)	191 (80,453)**	0·13 (0·03,0·53)	0·11 (0·04,0·35)**	0·61 (0·18,2·01)	0·60 (0·19,1·89)

*p<0·05, **p<0·01, by *t* test. Other differences not significant. Log values of respiratory system resistance, time constant, compliance were used in the statistical analysis.

Table 2 *Effects of endotracheal suction or lavage according to presence or absence of obvious mucus secretions. Values are mean (95% confidence limits) for pre- and post-treatment*

Procedure	*Secretions obtained*	*n*	*Respiratory system*					
			Resistance ($cmH_2O/l/sec$)		*Time constant (sec)*		*Compliance (ml/cmH_2O)*	
			Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*
Suction	+	8	214 (88,520)	174 (88,342)*	0·20 (0·06,0·60)	0·14 (0·04,0·51)*	0·88 (0·19,4·06)	0·83 (0·16,4·10)
	O	11	182 (84,396)	178 (87,361)	0·09 (0·03,0·29)	0·09 (0·03,0·24)	0·51 (0·21,1·25)	0·49 (0·18,1·18)
	Combined	19	195 (84,455)	178 (89,356)	0·13 (0·03,0·50)	0·11 (0·03,0·36)*	0·64 (0·17,2·40)	0·61 (0·16,2.36)
Lavage	+	7	457 (132,1578)	261 (86,789)**	0·21 (0·07,0·66)	0·12 (0·04,0·37)**	0·53 (0·28,0·99)	0·51 (0·41,0·66)
	O	6	158 (74,340)	170 (91,318)	0·10 (0·04,0·57)	0·11 (0·05,0·27)	0·62 (0·19,2·06)	0·65 (0·22,1·91)
	Combined	13	275 (62,1219)	213 (77,594)*	0·15 (0·04,0·56)	0·12 (0·04,0·32)	0·57 (0·22,1·47)	0·57 (0·26,1·26)

*p<0·05, **p<0·01, by *t* test. Other differences not significant. Log values of respiratory system resistance, time constant, and compliance were used in the statistical analysis.

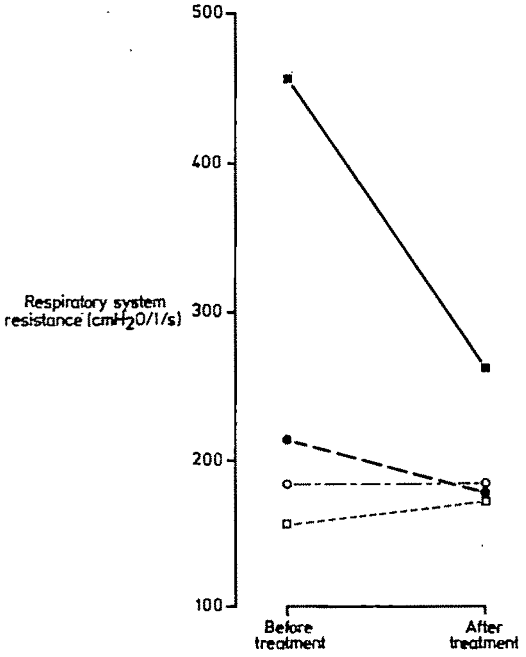

Fig. 1 *Changes in respiratory system resistance after suction (circles) and lavage (squares) according to whether secretions were obtained (closed symbols) or were not obtained (open symbols). There was a significant reduction in resistance when secretions were obtained by lavage ($p<0{\cdot}01$) or suction ($p<0{\cdot}05$).*

tendency for resistance to increase. Although there was a tendency for compliance to fall slightly after both procedures, no change was significant.

During the periods of continuous monitoring pronounced and consistent individual increases in resistance were occasionally seen, responding to tracheobronchial lavage (Fig. 2). In one individual an alarming increase in resistance indicated an urgent need to change a blocked endotracheal tube (Fig. 3).

Discussion

The adaptation of the single breath technique described by Zin *et al*[7] has provided a non-invasive means of monitoring the total respiratory system resistance. We have used this method to assess the timing and efficacy of routine tracheobronchial suction and lavage. Both of these procedures were effective in reducing resistance in patients whose resistance was abnormally high and in patients from whom visible secretions were removed by the procedures.

To obtain reference values for resistance in

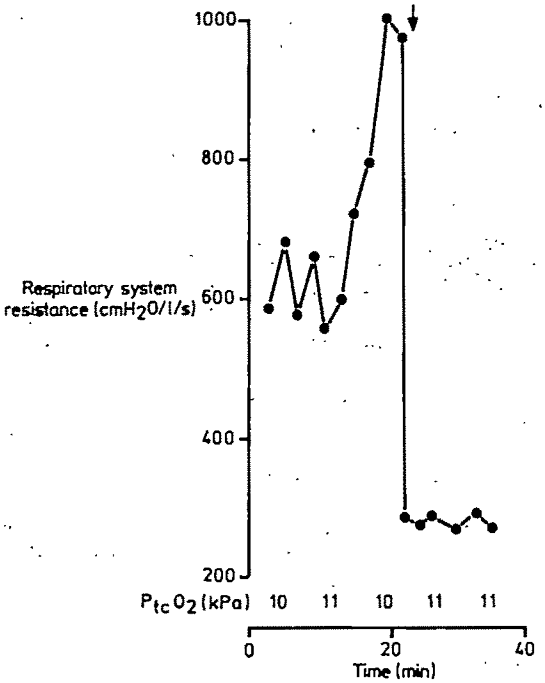

Fig. 2 *Changes in respiratory system resistance and transcutaneous oxygen tension ($P_{tc}O_2$) in one infant during 35 minutes of continuous monitoring. A sudden increase in resistance was restored to normal by bronchial lavage (indicated by arrow).*

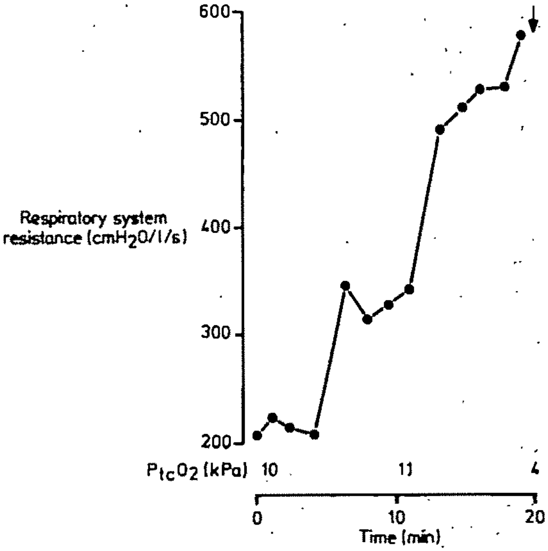

Fig. 3 *Progressive rise in respiratory system resistance, and transcutaneous oxygen tension ($P_{tc}O_2$) in one infant during 20 minutes of continuous monitoring. When removed (indicated by the arrow) the endotracheal tube was found to be completely occluded by mucus.*

intubated babies we studied a mixed group of mechanically ventilated, preterm infants over the first two days of life. The mean values of resistance were remarkably similar for infants with hyaline membrane disease and those with no respiratory tract disease and were close to the few published values for infants of this size.[8-10] While it is clear that smaller babies (with smaller airways and smaller endotracheal tubes) must have higher values of resistance than larger infants, the range of ages of infants in our reference sample was not large enough to provide size related values. Nor has any attempt been made to subtract endotracheal tube resistance as the tube is functionally a very important and easily obstructed part of the infant airway. The 'correction' for tube resistance would in any case be complex as tube resistance is flow dependent. Interestingly, despite this pronounced change in tube resistance with flow, in most cases the end expiratory flow-volume curves were linear, implying a single value for the time constant. It is known that the airways resistance tends to increase as the lungs deflate.[11] By coincidence, it seems that this effect may be balanced by the reduction in endoctracheal tube resistance as flow rates diminish during expiration.

By taking babies in their first two days of life, all of necessity older than 12–15 hours, as the reference population, we hoped to control for all the variables that might affect resistance, with the exception of airway secretions, which appear clinically to be unusual during the first two days of mechanical ventilation in preterm infants. The values of resistance obtained provided a useful basis for predicting the benefits of suction or lavage and in the babies who did require such treatment an increase in resistance was usually noted before changes in arterial oxygenation (Fig. 2), although it is possible that arterial carbon dioxide tension might have been a more useful indicator of decreased alveolar ventilation. We attribute the late changes in oxygen tension, even with quite large increases in resistance, to the very short expiratory time constants found in these babies.

In babies with airways disease this technique of measuring respiratory resistance has several disadvantages. Firstly, all babies with external air leaks such as pneumothoraces had to be excluded from analysis. Two babies were found to have leaks around their endotracheal tubes, as indicated by their failure to maintain an inspiratory volume plateau. Their data were also excluded from analysis. Secondly, this system could not be used for more than four continuous hours in the ventilator circuit because of condensation in the ventilator tubing, which affected the accuracy of the pneumotachographs. Thus continuous monitoring of resistance was not possible. Thirdly, in a small number of babies the relation between flow and volume between 50 and 97% of expired volume was not linear and therefore it was not possible to give a single value to resistance. It may be possible, however, to obtain some indication of respiratory resistance in such babies by observing the shape of the curve. Abnormally high resistance would be indicated by a flow-volume curve with a convex configuration towards the origin.

A major disadvantage is the need for passive expiration. Without oesophageal monitoring it may be impossible to exclude completely all respiratory effort. A linear expiratory flow-volume curve goes some way to confirming relaxation in intubated babies. The procedure that we sometimes used of hyperventilation to achieve apnoea by hypocapnia might affect resistance by altering bronchomotor tone.[12] This effect is likely to be trivial compared with the resistance changes due to secretions and their treatment. In spite of these potential drawbacks, we were able to make reproducible baseline measurements of lung mechanics using the single breath technique in babies with severe degrees of airways obstruction and to show changes after tracheobronchial toilet. Others have provided information using the same technique on the changes in resistance after extubation in the neonatal period.[10]

The benefits of tracheobronchial toilet were not universal. A balance is required between the potential benefits of removal of secretions (improved overall mechanical ventilation and more even distribution of ventilation) and the potential adverse affects (hypercapnia and hypoxia resulting from temporary ventilator disconnection, fall in compliance due to removal of positive pressure, and displacement of secretions into peripheral airways). When secretions were not obtained there was no change in resistance. One explanation is that the procedure itself was ineffective. This is unlikely as the mean value of resistance in the groups from whom no secretions were obtained after suction or lavage (Table 2) was close to the reference range. It seems likely, therefore, that these infants did not require 'routine' suction or lavage, with its potential adverse effects.

The level of resistance, in relation to a reference population, was a useful way of identifying patients with appreciable airway obstruction. After treatment resistance was almost halved in those with pretreatment values above the range of reference group. The change in time constant values was equally striking and of great clinical importance in this mechanically ventilated group.

The time constant indicates the rate of emptying of the lungs, assuming exponential flow. Thus the shorter the time constant the more rapidly expiration is completed. The value of the time constant is therefore vitally important during mechanical ventilation; a long time constant due to mucous obstruction, for instance, may cause air trapping during rapid frequency ventilation if the expiratory time is short.

The group with the most severe airways obstruction (Table 1) had a mean time constant of 0·30 seconds. The extent of passive expiration depends only on the time constant and duration of expiration: 97% of the total volume is exhaled in 3 × time constant. For infants with a time constant of over 0·30 seconds expiratory times of under 0·9 seconds may lead to air trapping. The current fashion for higher rates of mechanical ventilation might be hazardous in such patients. The fall in mean time constant to 0·12 seconds after tracheobronchial toilet was another measure of the success of the procedure.

There were no significant changes in compliance after any procedure. This is reassuring as both ventilator disconnection (by reducing the inflation pressure on the lungs) and displacement of secretions into peripheral parts of the lung might be expected to result in a fall in compliance. As compliance did not change and we made our measurements before and after suction under identical ventilator settings we assume that lung volume was also identical.

Potentially, continuous monitoring of resistance could obviate the sorts of crisis illustrated in Figure 3. The ideal equipment does not exist for measuring endotracheal tube flow, although it may be possible to obtain an index of resistance without inserting any device into the flow pathway.[13] We have indicated the potential advantages of continuous assessment of respiratory system resistance and the efficacy of a simple technique of tracheobronchial toilet. In the future a more satisfactory system for the long term monitoring of lung mechanics during mechanical ventilation may provide the basis for comparing different techniques of tracheobronchial care.

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Asthma education by community child health nurses

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SUMMARY A randomised controlled study of an educational programme for children with asthma and their families was carried out by community child health nurses. Three hundred and sixty eight children aged 2 to 14 years were enrolled in the study after admission to hospital for asthma. The intervention group was visited monthly by a nurse for six months. The subjects were assessed six months later by a postal, self administered questionnaire. European children in the intervention group were taking significantly more drugs for the treatment of asthma six months after the index admission to hospital than those in the control group (mean (SD) intake 2·7 (1·1) *v* 2·1 (1·0), respectively). In particular, they were using more theophylline (56·6% *v* 37·0%) and inhaled steroids (34·9% *v* 21·0%). There was no difference between the groups for parental reports of improvement, of missed schooling, and in severe attacks of asthma of not responding to the usual treatment at home. European children in the intervention group used the hospital services for severe attacks of asthma more than controls (34·2% *v* 10·5%). There were more re-admissions in the European intervention group in the subsequent six months after the index admission than in the control group (mean (SD) 0·51 (0·97) *v* 0·29 (0·65)). Re-admission continued to be higher in the 12 months after the nurse had stopped visiting (0·81 (1·65) *v* 0·25 (0·65)). There was no difference in the duration of hospital stay between the intervention and control groups. For Polynesian children there was no difference between the groups for any outcome measures.

Rates of admission to hospital for asthma in the 0–14 year age group have increased strikingly since the mid-1960s in New Zealand, the United States, Canada, England and Wales, and Australia.[1] Part of this increase is due to an increase in the re-admission rate.[2–4] In New Zealand both admission and re-admission rates are higher in Polynesian than in European children.[4 5]

An earlier study in Auckland showed that, compared with Europeans, Polynesians were using less drugs for asthma, particularly those used for prophylaxis, were more likely to run out of medication, and were referred to hospital more often by the accident and emergency department and less often by their general practitioner.[5] In England there has been a shift in the care of patients with asthma from primary care towards the hospital and also an increase in the number of self referred patients.[2 3] These patients tended to have less severe asthma on admission than patients referred by their general practitioner.

Asthma is underdiagnosed and undertreated,[6] and many paediatric admissions to hospital for asthma are, in some way, related to improper action taken by the patient, his family, or the health care professional.[7 8] A recently reported intensive programme designed to teach self management skills to 13 children with asthma and their parents by a specially trained nurse educator resulted in fewer admissions to hospital and emergency room visits compared with 13 control patients, less school absenteeism, and fewer attacks of asthma.[9] Although this programme has been shown to be effective, it would be expensive to implement for all patients with asthma.

The purpose of this study was to determine whether additional education of children with asthma and their parents by community child health nurses* in the patients' homes could alter the course of their disease. The specific aims of the study were to reduce school absenteeism, to encourage visits to their general practitioner, to reduce the number of re-admissions to hospital and to teach parents and the child when to start additional treatment and when to seek medical help for the attack of asthma not responding to the usual treatment.

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*Strictly speaking, the nurses were public health nurses employed by the Department of Health.

Patients and methods

Patients discharged from the paediatric medical wards of Auckland Hospital for asthma (ICD 493) over a one year period (from 15 April 1983 to 14 April 1984) were entered into the study. Patients aged less than 2 years and patients whose home was outside the hospital catchment area were excluded. A small number of patients with asthma who had had previous life threatening attacks were also excluded. All parents of the subjects completed a questionnaire on admission, which was based on previously published questionnaires concerning the child's medical history and social characteristics of the family.[10 11]

Patients were divided into two ethnic groups, (1) Polynesians, which included Maoris and Polynesian Pacific Islanders, and (2) Europeans, because there are considerable differences in the medical management of their asthma, rates of re-admission, and socioeconomic state.[4 5] Other ethnic groups were excluded. They were then randomised into an intervention or control group at the time of discharge from hospital. The patients and their families in the intervention group were visited monthly by a community child health nurse for six months. The intervention programme performed by the child health nurse was as follows.

(a) An explanation of the anatomy, pulmonary physiology, and pathophysiology of the lung and of the factors that can provoke asthma—for example, allergies, infections, exercise, and emotions.

(b) A description of the drugs used in asthma, especially those drugs prescribed for the child.

(c) Emphasis of the importance of avoiding stimuli that may provoke asthma and controlling the patient's environment—for example, measures to avoid home dust.

(d) A check on drug compliance (inspection of the contents of bottles of medicine to ensure drugs do not run out) and correct use of aerosols.

(e) Encouragement to attend follow up clinic visits to either the paediatrician at the paediatric outpatient clinic, if arranged, or to their general practitioner.

(f) Encouragement to consult their general practitioner rather than the accident and emergency department in the event of an attack of asthma not responding to treatment with bronchodilator at home.

No attempt was made to influence the type of treatment given to the child or the type of follow up received. The nurses contacted the child's general practitioner, however, to inform him of their involvement and to obtain up to date information on the patient and his family. The nurses were asked to keep a record of the number of patient/family contacts but were not asked to collect any other data.

Six months after discharge from hospital the child's progress and current management and family attitudes to their child's asthma and its management were examined, using a postal, self administered questionnaire. If a reply was not received a further copy of the questionnaire was sent. There were no further attempts after this to contact the family. In addition, the number of re-admissions and the duration of each re-admission to hospital for the six months after the index admission when the child health nurse was visiting and for the 12 months after the nurse had stopped visiting (six to 18 months after the index admission) were extracted from the hospital records. The last patient completed the 18 months' follow up on 14 October 1985.

Results are expressed as mean (SD) and were analysed using standard parametric and non-parametric tests of significance.

The study was approved by the Auckland Hospital ethical committee.

Results

Three hundred and sixty eight patients were entered into the study, of whom 200 were European and 168 Polynesian. There were 94 European children in the intervention group and 106 in the control group and 84 Polynesian children in both the intervention and control groups.

The age and sex ratio of European children (6·1 (3·4) years, male:female ratio 1·4:1) did not differ from that of Polynesian children (5·5 (3·0) years, 1·6:1). European children were significantly socioeconomically advantaged compared with Polynesians, as measured by the occupations of the parents, home ownership, and having their own bedrooms. On admission to hospital European children were taking a larger number of medications for asthma than Polynesians (1·8 (1·2) *v* 1·4 (1·3), respectively, $p<0·001$), and were significantly more likely to be taking cromoglycate, inhaled steroids, and sympathomimetics.

The child health nurses returned visit numbers on 135 intervention patients (76%). Of the returns, eight (6%) had no visits as the families could not be located, 35 (26%) had some but not all six of the monthly visits, and 92 (68%) had all six of the monthly visits.

Parents of the European children in the intervention group were more likely to return the second questionnaire than parents in the control group (88% *v* 76%, respectively, p=0·029). The respective percentage returns for Polynesians were 60% and 54% (not significant).

Tables 1 and 2 summarise the results of the intervention for the European and Polynesian children, respectively. European children in the intervention group were taking significantly more drugs for the treatment of asthma six months after the index admission to hospital than those in the control group (2·7 (1·1) *v* 2·1 (1·0), respectively, p<0·001). In particular, they were taking more theophylline (57% *v* 37%, p=0·012) and inhaled steroids (35% *v* 21%, p=0·047). There was no difference between the groups for parental reports of improvement, of missed schooling, and in severe attacks of asthma of not responding to the usual treatment at home. If the child had an attack of asthma not responding to usual treatment they were more likely to be taken to a general practitioner rather than the hospital (including the accident and emergency departments or directly to the children's wards), but the intervention group used the hospital service for primary care more often than the control group (34% *v* 11%, p=0·043). There were more re-admissions in the European intervention group in the subsequent six months after the index admission than in the control group (0·51 (0·97) *v* 0·29 (0·65), p=0·067), although the number of patients re-admitted in the intervention group did not significantly differ from the control group (30% *v* 21%). In the next 12 months, six to 18 months after the index admission, more patients were re-admitted from the intervention group than from the control group (32% *v* 16%, p=0·008) and the number of re-admissions was also greater (0·81 (1·65) *v* 0·25

Table 1 *Progress at six and 18 months after index admission to hospital for European children with asthma. Values are No (%) unless otherwise stated*

	Treatment group		
	Intervention	*Control*	*p Value*
Six months after index admission	(n=83)	(n=81)	
Current asthma drug treatment:			
Nil	0 (0)	6 (7)	0·012
Mean (SD) No	2·7 (1·1)	2·1 (1·0)	0·001
Sympathomimetics:			
Regular	42 (51)	33 (41)	NS
As required	58 (70)	49 (61)	NS
Total	76 (92)	69 (85)	NS
Theophylline:			
Regular	23 (28)	14 (17)	NS
As required	25 (30)	16 (20)	NS
Total	47 (57)	30 (37)	0·012
Cromoglycate:			
Regular	36 (43)	31 (38)	NS
As required	2 (2)	4 (5)	NS
Oral steroids:			
Regular	3 (4)	0 (0)	NS
As required	2 (2)	3 (4)	NS
Inhaled steroids:			
Regular	29 (35)	17 (21)	0·047
As required	1 (1)	2 (3)	NS
Other (ipratropium, antibiotics, cough mixture, antihistamines)	10 (12)	5 (6)	NS
Improved (%)	80	76	NS
Asthma attack not responding to usual treatment at home (%)	48	46	NS
Where this attack was treated (%):			
General practice	61	84	
Hospital	34	11	
Other	5	5	0·043
Mean (SD) days off school in previous six months	8·6 (15·1)	6·3 (8·8)	NS
Child knows how to prevent an attack of asthma (%)	30	37	NS
Parent knows when to start additional treatment (%)	96	98	NS
Parent knows when to seek further medical advice (%)	98	99	NS
Re-admissions in six months after index admission	(n=94)	(n=106)	
% Of patients	30	21	NS
Mean (SD) of re-admissions	0·51 (0·97)	0·29 (0·65)	0·067
Mean (SD) duration of hospital stay (days)	4·0 (7·7)	2·5 (1·5)	NS
Re-admissions between six and 18 months after index admission	(n=94)	(n=106)	
% Of patients	32	16	0·008
Mean (SD) of re-admissions	0·81 (1·65)	0·25 (0·65)	0·003
Mean (SD) duration of hospital stay (days)	3·1 (2·4)	3·1 (2·4)	NS

NS=Not significant.

Table 2 *Progress at six and 18 months after index admission to hospital for Polynesian children with asthma. Values are No (%) unless otherwise stated*

	Treatment group		
	Intervention	*Control*	*p Value*
Six months after index admission	(n=50)	(n=45)	
Current asthma drug treatment:			
Nil	3 (6)	5 (11)	NS
Mean (SD) No	2·0 (1·16)	1·98 (1·96)	NS
Sympathomimetics:			
Regular	25 (50)	14 (31)	NS
As required	20 (40)	28 (62)	0·031
Total	40 (80)	34 (76)	NS
Theophylline:			
Regular	14 (28)	9 (20)	NS
As required	9 (18)	11 (24)	NS
Total	23 (46)	19 (42)	NS
Cromoglycate:			
Regular	15 (30)	10 (22)	NS
As required	3 (6)	1 (2)	NS
Oral steroids:			
Regular	0 (0)	0 (0)	NS
As required	1 (2)	1 (2)	NS
Inhaled steroids:			
Regular	11 (22)	11 (24)	NS
As required	0 (0)	1 (2)	NS
Other (ipratropium, antibiotics, cough mixture, antihistamines)	3 (6)	4 (9)	
Improved (%)	86	82	NS
Asthma attack not responding to usual treatment at home (%)	49	44	NS
Where this attack was treated (%):			
General practice	47	65	
Hospital	47	30	
Other	7	4	NS
Mean (SD) days off school in previous six months	6·8 (6·6)	12·4 (25·2)	NS
Child knows how to prevent an attack of asthma (%)	39	24	NS
Parent knows when to start additional treatment (%)	96	98	NS
Parent knows when to seek further medical advice (%)	95	98	NS
Re-admissions in six months after index admission	(n=84)	(n=84)	
% Of patients	32	27	NS
Mean (SD) of re-admissions	0·48 (0·83)	0·38 (0·71)	NS
Mean (SD) duration of hospital stay (days)	2·7 (1·4)	3·5 (2·6)	NS
Re-admissions between six and 18 months after index admission	(n=84)	(n=84)	
% Of patients	32	33	NS
Mean (SD) of re-admissions	0·69 (1·34)	0·57 (1·10)	NS
Mean (SD) duration of hospital stay (days)	4·3 (3·9)	3·3 (2·1)	NS

NS=Not significant.

(0·65), p=0·003), but there was no difference in the duration of hospital stay. There were no deaths in either group.

For Polynesian children there was no difference between the intervention and control groups for any of the outcome measures made six months after the index admission. Also there was no difference between the groups in re-admissions or duration of hospital stay six to 18 months after the index admission. Again there were no deaths in either group.

Discussion

Asthma is one of the most common diseases in childhood. Estimates of the prevalence of asthma in New Zealand have yielded results ranging from 1·9%[12] to 25%,[13] and this seems to be increasing.[14] This difference almost certainly reflects differences in the classification of asthma and wheeze. Although death is rare in childhood,[15] it is an important cause of admission to hospital[1] and morbidity.[6 16] Community studies show that asthma is underdiagnosed and undertreated[6 17] and that children with asthma are also often absent from school because of ill health.[13 18]

In this study the children were having frequent attacks of asthma (an average of 13 each year, lasting on average two days), were missing an average of three and a half weeks of school because of asthma, and by the completion of the study had had an average of 5·3 admissions to hospital for asthma.

In New Zealand in 1983 there were 5240 admissions in the 0–14 year age group, a rate of 634 per 100 000 population.[19] Re-admissions for asthma are common[3–5 8] and are increasing.[3 4] Rate of re-admission are higher in Polynesian than European children.[4] This study confirms this finding; 49% of European children were first admissions for asthma compared with only 31% of Polynesian children. A reduction in the rates of re-admission would markedly reduce the total number of admissions to hospital for asthma.

Teaching self management skills to children with asthma and their parents by a specially trained nurse educator is effective in reducing admissions to hospital for and morbidity from asthma.[9] Providing such a service for all children with asthma, however, would be prohibitively expensive. Accordingly we used the existing community nursing services—namely, public health nurses employed by the Department of Health. An important aspect of their role is the continuing care of children in schools and the community. The nurses were given additional training on asthma by one of us (EAM).

The study would have been more powerful if we could have included a wider range of outcome measures. Ideally, daily asthma diaries and measurements of peak expiratory flow would have been used; they could not be included in the control group, however, without possibly having some beneficial effect of their own. The outcome variables therefore chosen were hard data, such as re-admissions, missed schooling, and parental reports of the medical management of their child's asthma and their perception of their own and their child's management skills.

The study found that European children in the intervention group were taking significantly more drugs for asthma six months after the index admission to hospital than in the control group. More were taking medications for asthma in each drug category (with preventative drugs, theophylline, and inhaled steroids reaching significance). This result probably represents improved compliance. This increased use of medications, however, was not associated with an increased parental report of improvement, a reduction of missed schooling, or a reduction in attacks of asthma not responding to the usual treatment at home. The nurses were asked to encourage the families to use their general practitioner rather than the accident and emergency departments for severe attacks of asthma. The result of the intervention was the converse of this, with 34% in the intervention group using the hospital services when they had a severe attack compared with only 11% in the control group ($p=0{\cdot}043$). A possible explanation for this unexpected finding was that the nurses taught the children and their parents to take attacks of asthma seriously, to seek medical help early, and if their general practitioner was not readily available to go directly to hospital for treatment of the attack of asthma not responding to the usual treatment. The parents' perception of their knowledge of when to begin additional treatment for asthma and when to seek further medical advice was uniformally high in both the intervention and control groups and did not differ statistically. The result that was unexpected and of most concern was that re-admissions in the next six months, when the nurse was visiting, and between six and 18 months after the index admission were greater in the intervention group than in the control group. Although this was the opposite to our original aim, it could be argued that this was beneficial and that this high risk group of patients were making more effective use of the available facilities.[20] These admissions to hospital did not result, however, in a shorter duration of stay.

Polynesians have higher mortality[12] and rates of admission to hospital for asthma.[4] They also tend to have poorer health than Europeans on a number of health indices.[21] It is well known that Polynesians make poor use of the available health services, which has many similarities to the National Health Service in the United Kingdom. As less than 60% of the Polynesian parents returned the postal questionnaire six months after the index admission the results of the intervention have to be interpreted with caution. We were unable to show, however, that intervention influenced any of the outcome variables. In contrast to the European subjects, there was no effect on re-admissions in the intervention group.

Other recently reported evaluations of programmes of patient education for children with asthma and their parents suggest that these programmes can reduce school absenteeism, emergency room visits, and admissions to hospital and improve activity.[22,23] The subjects from these other trials were enrolled from clinics[9,23] or in response to media advertisements.[22] Our subjects were enrolled at the time of the admission to hospital and in comparison to the subjects in these other studies had more severe asthma. Admission to hospital is almost certainly a major intervention in itself as all children admitted with asthma are seen by a paediatrician and treatment is rationalised, inhaler technique checked, compliance assessed, and a crisis plan devised. This major educational opportunity occurred for all patients in both the intervention and control groups and many have diminished the beneficial effect of the educational programme carried out by the child health nurse.

These results were discussed with the nurses involved in the study. A valid criticism was that the outcome measures did not cover areas where they thought they had produced the greatest improvement, such as the child's activity and well being, parental knowledge, and ability in handling an asthmatic crisis.

Less than 5% of children were taking systemic prednisone before admission to hospital. Although this study did not attempt to influence the type of treatment given to the child, the use of short courses of oral steroids begun by the parents may have prevented some of the original admissions to hospital and subsequent re-admissions. This is worthy of future study.

The study indicates that it is possible to improve compliance with treatment for asthma by using nurse educators, but improved compliance and education in themselves may not necessarily reduce admission to hospital and school absenteeism in the high risk child with asthma. Further educational programmes need to be developed and the delivery of culturally relevant health care to Polynesians improved.

We thank the public health nurses of the Takapuna, Auckland, and South Auckland Health Districts for carrying out the intervention programme and the paediatricians of Auckland Hospital for allowing us to study their patients. We also thank Mr P Flynn for additional statistical analysis. Permission to publish from the Director-General of Health is acknowledged.

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Synchronous mechanical ventilation of the neonate

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SUMMARY We describe a simple technique of neonatal ventilation that induces the neonate to breathe in synchrony with the ventilator. This preserves the beneficial effects of spontaneous respiration (unlike therapeutic paralysis) and reduces potentially harmful interactions between baby and ventilator. The technique uses measurements of the neonate's own respiratory timing.

Unless paralysed or very ill, most ventilated neonates continue to breathe, but often out of step with the ventilator.[1]

The neonate's respiratory efforts can make a considerable contribution to ventilation but can also reduce the efficacy of ventilator treatment and increase the risk of pneumothorax.[2]

Spontaneous inspiration or expiration during the 'deflation' phase of a constant flow ventilator should be harmless. It is when spontaneous expiration is active and takes place during the 'inflation' phase of the ventilator that the baby can reduce the tidal volume delivered by the ventilator and when pneumothorax is most likely to occur.[2] We have used the term 'active' in this paper to represent the pattern described as such in previous work but acknowledge the fact that an active component to expiration in this situation awaits confirmation.

Past attempts to deliver synchronous mechanical ventilation have relied on devices triggered by the patient.[3] This is technically difficult in the preterm neonate as it relies on detecting small fluctuations in airway pressure generated by the patient. It is difficult to produce a ventilator sensitive enough, or with short enough response times, to produce phase synchrony.[4] Others have ventilated babies with respiratory rates that crudely approximate to the spontaneous respiratory rates of the baby, but they have not studied the patterns of interaction between baby and ventilator.[5] [6] We have observed that many babies attempt to maintain their own respiratory pattern when subject to mechanical ventilation. In some babies respiratory reflexes are observed that modify this pattern during certain ventilator breaths.[7]

We see potentially harmful asynchronous respiration occurring in one of two ways. Firstly, the neonate may breathe with a respiratory rate different to the ventilator or with an irregular rhythm. Secondly, the neonate may breathe at the same rate as the ventilator but with inspiration and expiration out of phase. Both patterns result in spontaneous expiration during the inflation phase of the ventilator.

When the neonate and the mechanical ventilator are 'breathing' at the same rate they are 'rate matched'. When the inflation and deflation phases of the ventilator coincide exactly with those of the baby they have 'phase synchrony'. When the ventilator and baby are breathing exactly in time with each other they are therefore rate matched and in phase synchrony. We have investigated the effects of matching the intrinsic respiratory timing of the baby with the ventilator settings.

Patient and methods

We describe the technique in a baby of 32 weeks' gestation, weighing 1800 g, ventilated as treatment for respiratory distress syndrome, using the Sechrist Model IV-100B infant ventilator. We have successfully used the technique in babies of various gestational ages, ventilated for respiratory distress syndrome and other conditions, employing the Sechrist, Bourns BP200, and SLE Newborn 250 infant ventilators. The Sechrist ventilator has the advantage that inflation and deflation times can be directly and independently set on the ventilator without reference to calculations involving rate and inspiratory:expiratory ratio. It also maintains constant 'peak', 'end', and 'mean' airway pressures at physiological respiratory rates. The technique could be used, however, with any time cycled ventilator that can deliver high ventilation rates and maintain airway pressures at these rates.

The baby's own respiratory efforts were continuously recorded using a pneumatic capsule device (the MR10 Respiration Monitor, Graseby Dynamics

Ltd). When taped in the sub-xiphisternal position this provides a signal qualitatively representing the baby's spontaneous respiratory efforts with no interference from ventilator inflations as it differentiates ventilator from spontaneous breaths by the presence of xiphisternal retraction.[8] A similar signal could be obtained, more invasively and with greater difficulty, from measurement of oesophageal pressure or diaphragmatic electromyogram. This signal was used to measure the baby's own inspiratory and expiratory times and also, by comparing it with the ventilator circuit pressure signal, to show the time relation between spontaneous breaths and ventilator inflations.

A pneumotachograph in series with the endotracheal tube allowed measurement of gas flow in and out of the lungs. The flow signal was electronically intregrated to give tidal volume. This has been used to show the effect of the ventilator and the baby's own respirations on gas flow and tidal volume. Ventilator circuit pressure was measured at the proximal end of the endotracheal tube.

The signals were recorded on a Gould 2600S, rectilinear, six channel paper chart recorder, with a full scale deflection frequency response of 50 Hz, at a paper speed of 25 mm per second. Pressure transducers and pneumotachograph were produced by Mercury Electronics Ltd and the electronic integrator used to produce tidal volume signals was from the Gould 4600 series.

Results

A polygraphic record from the ventilated baby at 4 hours of age is shown in Figure 1.

The baby was receiving mechanical ventilation as follows: rate 40 breaths/minute (inflation time 0·48 seconds, deflation time 1·02 seconds). Peak pressure was 32 cm H_2O and end pressure 4 cm H_2O, with inspired oxygen=80%. Arterial blood gases were within the normal ranges.

It can be seen from the capsule trace that the baby was breathing irregularly and was therefore neither rate matched nor in phase synchrony with ventilator cycles. Flow and tidal volume traces showed that the baby's respiratory efforts were disturbing smooth tidal ventilation. Thus tidal volumes were erratic and bore little relation to ventilator timing. During most ventilator inflation phases, gas flow down the endotracheal tube was stopped before the end of the peak pressure plateau. During the first ventilator inflation shown in this section, gas was seen to flow up the endotracheal tube against the peak inflation pressure. Analysis of the capsule signal showed spontaneous expiration at this point, suggesting active expiration.

Having observed this pattern of asynchronous ventilation, we attempted to induce synchrony. The ventilator was switched from intermittent positive pressure ventilation to provide continuous positive airway pressure, with the baby breathing spontaneously for several seconds while recordings were made. From this a period of regular respiration was chosen and the mean inspired and expired times from five spontaneous breaths were calculated from the pneumatic capsule trace. In the case of this baby the calculated times were inspired time 0·28 seconds and expired time 0·32 seconds (rate=100 breaths/minute).

On returning to intermittent positive pressure ventilation the calculated inspiratory and expiratory

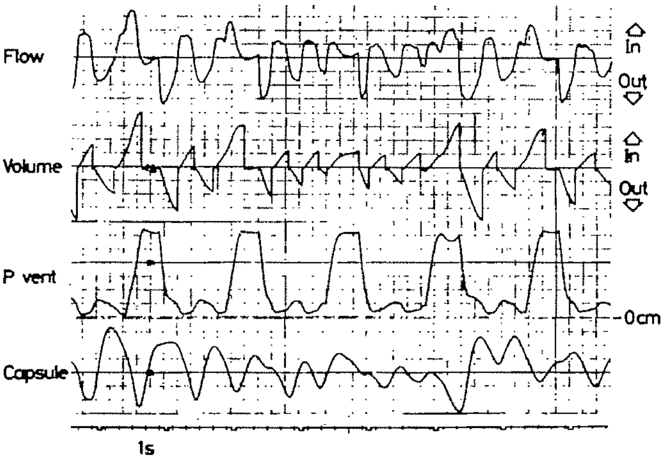

Fig. 1 *Asynchronous ventilation at a rate of 40 breaths/min. The top trace shows gas flow and the second trace tidal volume. Deflections above the centre zero line represent flow into the chest and those below the line flow out. The integrator resets to zero at zero flow. The third trace shows the pressure in the ventilator circuit (P vent) and the fourth trace the signal from the pneumatic capsule, with inspiration represented by a downward deflection on the trace, and expiration by an upward deflection.*

times were used as the ventilator settings. This provided a starting point for synchronisation. This results in rate matching, even if the baby was previously breathing irregularly. It does not always produce perfect phase synchrony, however, as the rate of change in lung volume is increased slightly by the positive inflation pressure. This is shown by analysing the ventilator circuit pressure and capsule traces together and shows whether there is phase synchrony. Small alterations in the ventilator time settings can be made to bring the two into phase. For example, if spontaneous expiration begins before the end of the peak pressure plateau the ventilator inflation time can be reduced until the inspiratory times are equal.

Figure 2 shows phase synchrony achieved in the same baby with inflation and deflation times both 0·3 seconds. There is rate matching and almost perfect phase synchrony; chaotic tidal volumes and episodes of active expiration against ventilator inflation are no longer apparent. Notice how smooth the pneumatic capsule trace has become. It was possible to reduce peak ventilator pressure to 23 cm H_2O while keeping arterial blood gases within the normal range.

Figure 3 shows tidal volume and pneumatic capsule signals during two periods each of about half an hour. This shows that the patterns of interaction described are not brief episodes produced by chance but are continuous. Once achieved, synchronous ventilation has persisted for many hours in some babies. In the lower record a period of asynchronous ventilation is seen, at the right hand end of the trace, which followed disturbance for a nursing procedure (rectal thermometer inserted at time indicated by arrow). When left undisturbed the baby is seen to settle back quickly into synchrony.

By 48 hours of age the lung disease had improved and ventilator pressures had been reduced (peak 18 and end 3 cm H_2O), as had inspired oxygen concentration. The baby had remained well synchronised with mechanical inflation and was ready to be weaned from the ventilator. Instead of arbitrary stepwise reductions in ventilator rate, as is often used in rate weaning, the ventilator was set to allow for one complete spontaneous breath and one ventilator synchronised breath, producing 2·1 rate matching between baby and ventilator (Fig. 4). There remained good phase synchrony during the concurrent breaths. This was produced using an inflation time of 0·34 seconds and a deflation time of 1·16 seconds. These figures were obtained from a short period of spontaneous breathing on continuous positive airway pressure, setting the inflation time on the ventilator to that taken spontaneously and the deflation time to that calculated to allow for one full spontaneous respiratory cycle plus expiration from the 'assisted' inflation. As before, it may be necessary to make small alterations in ventilator times to produce exact phase synchrony.

On 36 occasions when babies were breathing asynchronously with the ventilator, at rates of 75 per

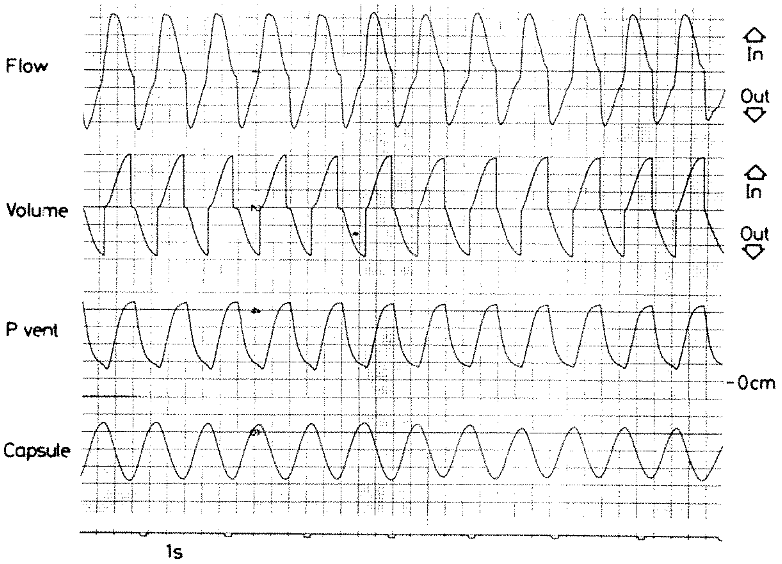

Fig. 2 *Established synchronous ventilation at a rate of 100 breaths/min. See Figure 1 for details of signals.*

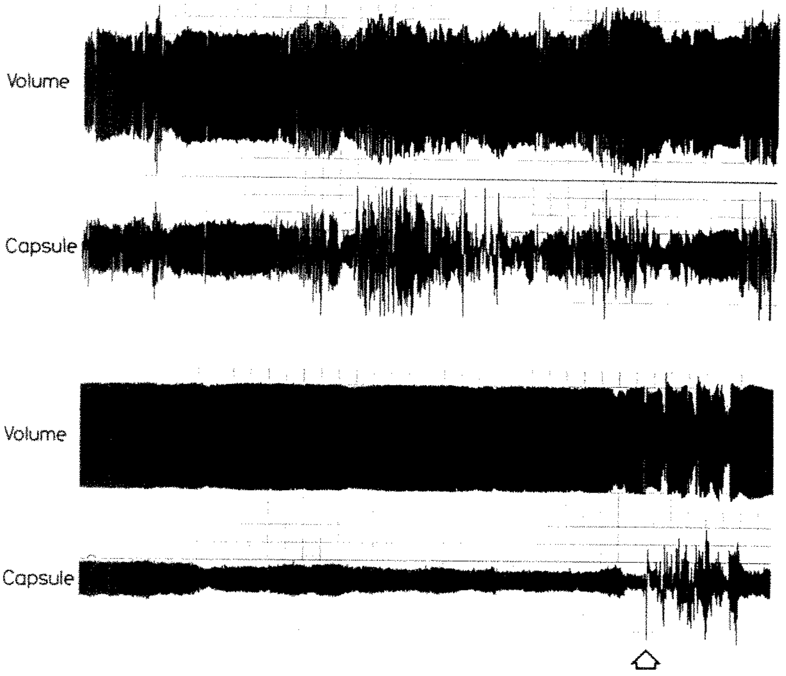

Fig. 3 *Tidal volume and pneumatic capsule signals during two half hour periods. The upper pair of traces show the tidal volume and capsule signals during the earlier period of asynchronous ventilation (as in Figure 1) and the lower pair during synchronous ventilation (as in Figure 2). The arrow represents the time of a nursing procedure.*

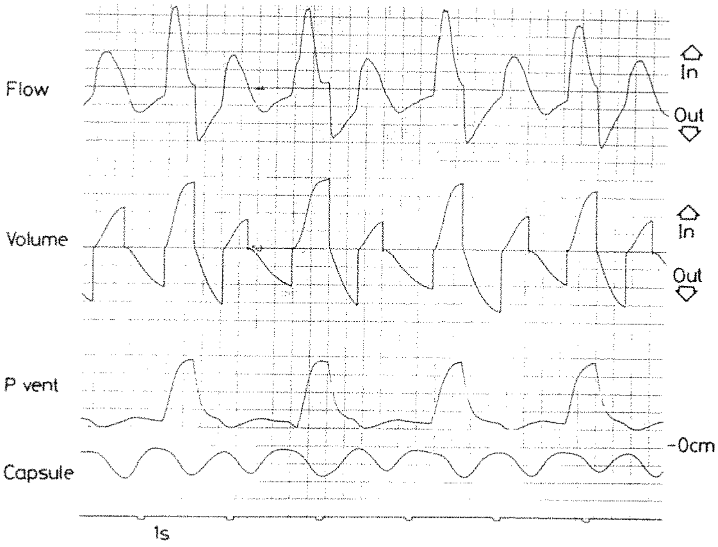

Fig. 4 *Rate matching of 2:1 (baby:ventilator) during weaning from ventilator. See Figure 1 for details of signals.*

minute or less, the degree of synchrony and the amount of expiration during ventilator inflation was improved in all cases by this technique. On most occasions stable synchronous ventilation was established, but in two babies, who were particularly irritable, synchrony was only maintained for short periods of up to 30 minutes. One of these babies was sedated with intravenous diazepam for clinical reasons and was noted thereafter to establish stable prolonged synchrony.

We have now synchronously ventilated over 20 babies for their entire course on the ventilator as treatment for respiratory distress syndrome. There has been one case of pneumothorax, in a baby ventilated with peak ventilator pressure of 40 cm H_2O, who had severe 'persistent transitional circulation' in association with respiratory distress syndrome.

Discussion

We have shown a technique that may be used in babies that breathe asynchronously while receiving mechanical ventilation—that is, babies who are often said to 'fight' the ventilator. In most babies the technique results in smooth synchronous ventilation with few episodes where the baby expires during the inflation phase of the mechanical ventilation.

The method uses a simple idea that takes as a starting point for ventilator settings the spontaneous respiratory timing of the baby and makes small adjustments, if necessary, to result in synchronous delivery of mechanical inflations. It is not surprising that the ventilator timing required to produce synchrony may differ slightly from that found during spontaneous breathing on continuous positive airway pressure as the inspiratory and expiratory time constants and the rate of change in lung volume are likely to be affected by the different tidal volumes and the presence of the inflating pressure.

The technique relies on making measurements of the baby's own respiratory timing. In this paper we have included signals from a pneumotachograph in the endotracheal tube to show the consequences, in terms of tidal volume, of the interaction of the ventilatory efforts of the baby and the ventilator. This should not be necessary in applying the technique clinically as all the information could be obtained from the non-invasively acquired signals of ventilator circuit pressure and the pneumatic capsule.

It would be simpler if a rule of thumb could be devised for ventilator time settings that are likely to produce synchrony as this would dispense with the need for measurements from the baby. Unfortunately, spontaneous respiratory times vary with a number of factors—for example, gestation,[9] severity of respiratory distress syndrome, age, and size of endotracheal tube. It may be that some of these factors would need to be considered in predicting the best times to use. Our preliminary evidence suggests that for preterm neonates with respiratory distress syndrome in the first 24–48 hours of age, inflation times in the range 0·28–0·35 and expired times in the range 0·35–0·45 are most likely to be suitable. The times required will probably vary in any given baby as the respiratory time constants follow changes in respiratory compliance and the course of the respiratory distress syndrome.

Recent work failed to show that the arbitrarily chosen rates of 60 or 120 breaths per minute would consistently produce synchrony in those babies previously found to be actively expiring against the ventilator at rates of 30 to 40. At the higher rates, however, the amount of active expiration was reduced by 88%. (Greenough A, Morley CJ, Pool J. Are fast rates and alternative to paralysis. Presented at the European Society for Pediatric Research, 1985:abstract 145.)

We have not studied the influence of such factors as blood gases, ventilator pressures, or neurological state on the development of synchronous ventilation, but these are likely to be important.

Does synchronous ventilation offer any advantages? The fact that it prevents expiration against ventilator inflation, which has been shown to be a factor in the production of pneumothoraces,[2] should be of importance. It may reduce the need for therapeutic paralysis. Heicher *et al* and Pohlandt *et al* have shown a reduced incidence of pneumothorax in babies ventilated at fast rates with short inflation times.[10] (Pohlandt F, Bernsau U, Feilen KD, *et al.* Reduction of barotrauma in ventilated neonates by increase in ventilation frequency. Presented at the European Society for Pediatric Research, 1985:abstract 144.) This would seem to be at variance with theories suggesting that high rates produce 'inadvertent positive end expiratory pressure' at distal airway level.[11] [12] These theories, based on respiratory time constant analysis, only consider the static lung and ignore the effects of spontaneous respiratory effort on respiratory time constants and rate of change in lung volume. It may be that in the studies of Heicher *et al* and Pohlandt *et al* there were fewer pneumothoraces in the fast rate groups because more babies were breathing in synchrony with their ventilators, as the fast rate groups received ventilator timing similar to that we use to produce synchrony. Unfortunately, these factors were not studied. In our babies the incidence of pneumothorax has been low so far (one out of over 20 babies), but this observation needs further investigation by means of a prospective, randomised, controlled trial.

There are theoretical advantages from synchronous mechanical ventilation in terms of cardiac output. Mean intrathoracic pressure is higher during asynchronous controlled ventilation than during synchronous assisted ventilation,[13] and this may reduce cardiac venous filling. Asynchronous controlled ventilation results in random swings in intra-atrial pressure, whereas synchronous ventilation results in a more physiological haemodynamic situation.[14] This may also have implications for the babies at risk from intracranial haemorrhage.[15]

Preliminary evidence we have from the babies we have studied shows an upward trend in minute ventilation with a consequent improvement in blood gases when the baby is breathing in synchrony with its ventilator but not when he is breathing in asynchrony. There may also be advantageous consequences of synchronous ventilation in terms of energy expenditure. Anecdotally, our nursing staff report that the baby who is breathing asynchronously is usually fractious and often struggles a lot, while the baby who is synchronously ventilated is often quieter and 'easier to nurse'.

We have noticed several other phenomena during synchronous ventilation. The baby who was breathing irregularly, both during asynchronous ventilation and during short periods of spontaneous breathing on continuous positive airway pressure, often breathed regularly and continuously once established on synchronous ventilation. The baby who was well synchronised on mechanical ventilation rapidly re-established phase synchrony after a period with intermittent positive pressure ventilation switched off, no matter at what phase of the spontaneous respiratory cycle ventilation was restarted. These phenomena of rate and phase entrainment have been observed in anaesthetised cats subject to mechanical ventilation[16] and are probably vagally mediated.

The process of rate weaning from the ventilator can be modified to produce synchronous ventilation as described. It is possible to produce various patterns of synchrony—for example, 2:1 and 3:1 rate matching between baby and ventilator. This may well provide for a more logical method of weaning, avoiding episodes of active expiration against ventilator inflation, than the arbitrary stepwise reductions in rate that are often made.

Studies of ventilator regimens that ignore the effects of spontaneous respiration may fail to recognise important factors. Ventilated babies, even those with the same disease, do not form a single homogenous group as they may be paralysed, apnoeic, or breathing synchronously with the ventilator.

We have shown that it is possible to induce synchronous ventilation by this technique. Whether it does offer the potential advantages outlined awaits further investigation.

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Periventricular leucomalacia and intraventricular haemorrhage in the preterm neonate

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SUMMARY Two hundred very low birthweight infants were prospectively scanned to ascertain the incidence of periventricular leucomalacia (PVL) and haemorrhage. Before collection of data, clear definitions of ultrasound abnormalities believed to represent PVL and intraventricular haemorrhage were described. These referred to small and moderate intraventricular haemorrhage, parenchymal haemorrhage, and PVL, including prolonged flare (echoes in the periventricular region lasting for two weeks or more and not becoming cystic). Sixty nine infants (34%) had no abnormality on ultrasound scans. Intraventricular haemorrhage occurred in 107 babies (37 grade I and 62 grade II), and only eight infants were thought to have true parenchymal haemorrhage. Ultrasound appearances of PVL were seen in 27 infants, 19 of whom developed cysts and eight died in the precystic stage. Prolonged flare occurred in another 25 babies. Unilateral parenchymal haemorrhage occurred in four infants who subsequently developed cystic PVL in the contralateral hemisphere. Twenty one infants developed ventricular dilatation, 12 of whom had associated parenchymal lesions. Haemorrhage, PVL, and flare occurred commonly in infants of 30 weeks' gestation and below and became markedly less common in more mature infants. We believe prolonged flare represents a form of PVL, and in this study a total of 52 (26%) infants had an ultrasound appearance of periventricular leucomalacia, an incidence considerably higher than previously reported.

Haemorrhage in and around the lateral ventricles is a common lesion of the preterm brain, with an incidence variously reported between 32%[1] and 90%.[2] Periventricular leucomalacia (PVL) has also been recognised as affecting the infant's brain, but its incidence has been largely derived from postmortem studies and may not reflect its incidence in surviving infants. High resolution real time ultrasound enables a diagnosis of PVL to be made in the living infant,[3–11] but there have been only three studies reporting its overall incidence,[4 5 11] which ranges between 7·5% and 17·8% of low birthweight populations. Preliminary data suggest that PVL is associated with a poor prognosis[6 7 12–14] and for this reason deserves more careful study. No agreed definitions exist for the ultrasound appearances of PVL, and as a preliminary to our study we carefully described the appearances that we believed represented ischaemic brain lesions. We then prospectively examined 200 very low birthweight infants to define the incidence of this condition, assess pathological correlation with scan findings, and look at risk factors for development of PVL and its effect on neurodevelopmental outcome. This paper compares the incidence of PVL with intraventricular haemorrhage in a group of infants weighing 1500 g or less at birth.

Patients and methods

Over a 16 month period (1 January 1984–30 April 1985) all neonates of birth weight ≤1500 g who were admitted to two neonatal intensive care units (Leicester Royal Infirmary and Nottingham City Hospital) were scanned at least twice each week for the first month and then once each week until discharge. All babies with an abnormality on the predischarge scan were recalled for at least one further scan. In both centres an ATL Mark III real time sector scanner fitted with a 3·5, 5, and 7·5 MHz multifrequency scanhead was used, and all scans were performed by the same observer (JQT). A permanent record of all scans was kept on either videotape or *x* ray film, and abnormalities were reviewed by another of the authors (MIL).

Definition of scan abnormalities. At the start of the study we clearly defined the ultrasound abnormalities we had consistently recognised over the previous three years. These definitions were adhered to throughout the study and final diagnosis was made at discharge or death. The definitions were as follows:

Normal
No ultrasound abnormality detected at any time.

Small haemorrhage
Echoes in and around the region of the germinal matrix and corresponding to the grade I haemorrhage of Levene *et al.*[10]

Intraventricular haemorrhage
Echoes within the lateral ventricles with distension or formation of an intraventricular clot. This corresponds to the grade II lesion of Levene *et al.*[10]

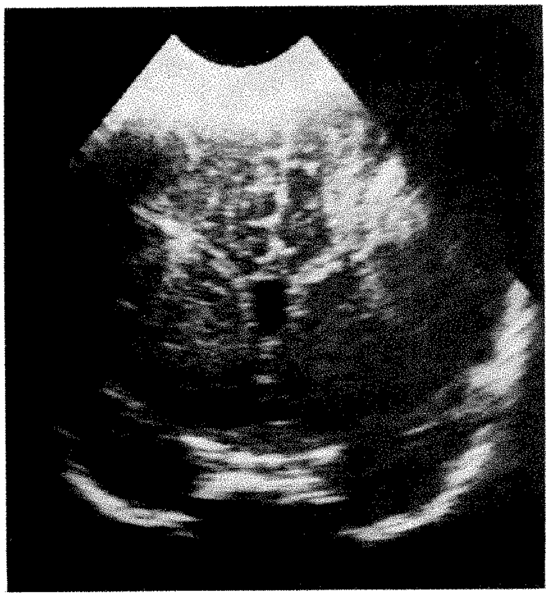

Fig. 2 *Periventricular leucomalacia. Coronal ultrasound scan showing a triangular echodense area with its apex lying at the lateral margin of the right lateral ventricle. There is a less extensive, but smaller, echodensity in the left sided parenchyma.*

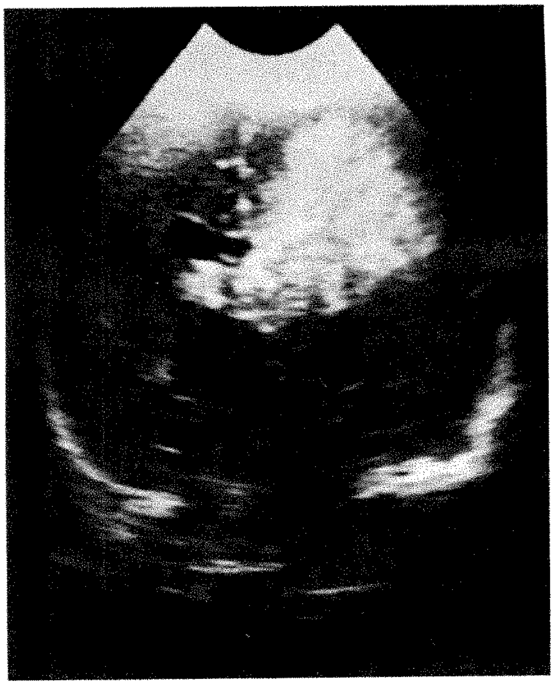

Fig. 1 *Parenchymal haemorrhage. Coronal ultrasound scan showing a large echodense lesion involving the right lateral ventricle and parenchyma. There is complete loss of the outline of ventricular structures.*

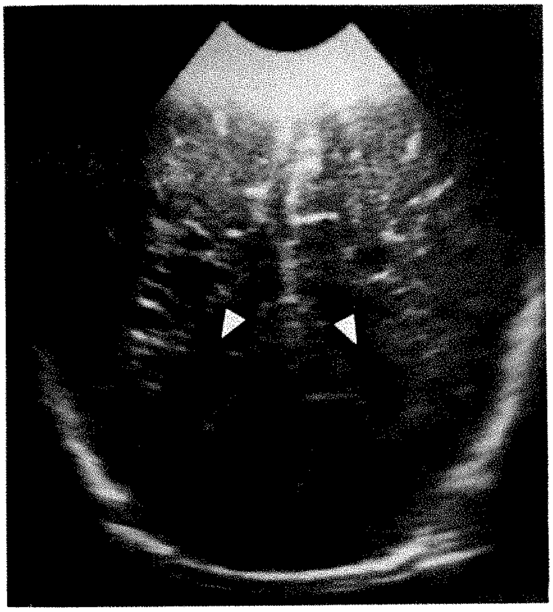

Fig. 3 *Cystic degeneration. Posterior coronal ultrasound scan showing bilateral and multiple echofree lesions separate from the lateral ventricles (arrow head).*

Parenchymal haemorrhage
An echodense area involving the ventricle and the parenchyma. The apex of the echoes lies near the midline with the base extending well into the parencyhmal substance. There is complete loss of the outline of ventricular structures (Fig. 1). In surviving infants a porencephalic cyst would develop with complete loss of the ependyma of the lateral part of the lateral ventricle. We refer to this lesion as representing 'parenchymal haemorrhage'.

Periventricular leucomalacia (PVL)
We recognised three appearances that we believed represented the range of PVL.

(a) Cystic. An echodense triangle with its apex lying at the lateral border of the lateral ventricle. In many infants intraventricular clot is seen within the ventricle and accompanies this parenchymal appearance. The triangular parenchymal appearance has been recently described by Rushton *et al*,[8] and we refer to it as 'PVL' (Fig. 2). In surviving infants the echodensity resolves to discrete echofree cavities representing cyst formation (Fig. 3). The ependyma of the lateral ventricles remains intact in most cases.

(b) Precystic. Some infants die in the precystic (echodense) phase, and if the ultrasound appearances described above are present at death this is referred to as precystic PVL.

(c) Prolonged flare. An appearance of relative increased echodensity in the periventricular region seen in both coronal and parasagittal views and persisting for at least two weeks but not undergoing cystic degeneration (Fig. 4). Although subjective assessment of echodensity is difficult, these lesions are less echogenic than those of parenchymal haemorrhage, despite standardised gain and energy output settings.

Ventricular dilatation
(a) Progressive. Ventricular index rapidly increasing to cross the 97th centile line.[16] This usually required treatment with lumbar punctures or a ventricular shunt.

(b) Persistent but non-progressive. Ventricular index increasing more slowly to cross above the 97th centile line but then arresting and following a normal rate of growth.

Babies with ventricular index greater than the 97th centile due to distension with echodense haemorrhage, and who subsequently return to normal measurements of ventricular index, were not included in the ventricular dilatation group.

Results

Of the 209 babies of birth weight ≤1500 g, seven were excluded because they died before a scan could be performed and two because they were transferred from outlying hospitals too late for a scan to

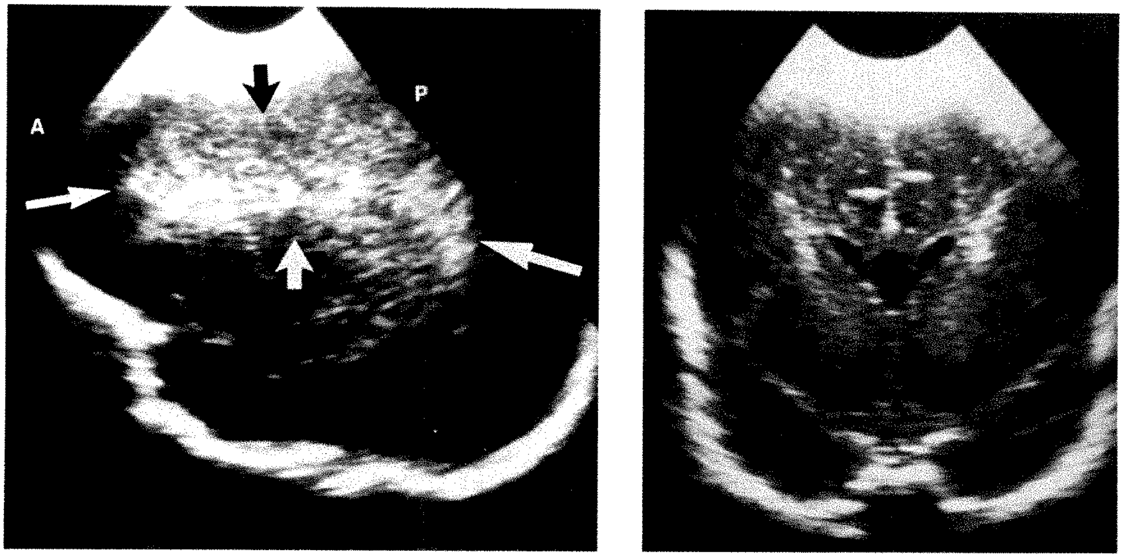

Fig. 4 *Echodense flare. Coronal ultrasound scan (right) showing discrete bilateral echodense areas in the periventricular region. There is no intraventricular haemorrhage. Parasagittal scan (left) showing extent of the flare (arrows) extending from the frontal region to the occipital region. A=Anterior, P=posterior.*

be performed within the first four days of life. The remaining two hundred infants form the subject of this report. Median birth weight was 1200 g (range 650–1500 g) and median gestational age was 29 weeks (range 25–37 weeks). Fifty six infants had a birth weight ≤1000 g.

Sixty nine infants (34%) had entirely normal scans.

Haemorrhage. Haemorrhage was seen in 107 babies (53%), and in 37 this was in the region of the germinal matrix (grade I haemorrhage). Grade II lesions occurred in 62 babies, and in a further eight there was parenchymal haemorrhage.

Parenchymal haemorrhage and PVL. Of the eight babies with parenchymal haemorrhage on early scans, four subsequently developed echodensity in the contralateral periventricular region after a variable period (Fig. 5). In the two long term survivors the former lesion resolved, with the formation of a large porencephalic cyst, and the latter into multiple discrete cysts. We believe this appearance represents parenchymal haemorrhage on one side with contralateral PVL. One infant had a prolonged flare of the opposite side; in only three babies with parenchymal haemorrhage was there no associated contralateral parenchymal lesion.

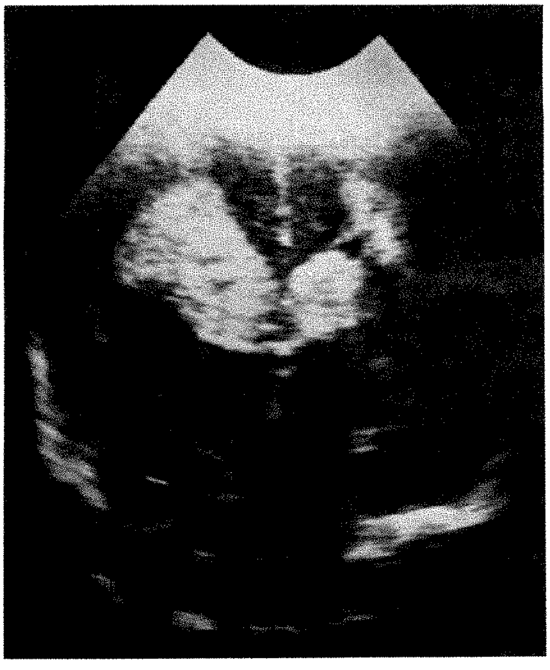

Fig. 5 *Parenchymal haemorrhage with contralateral periventricular leucomalacia. Coronal ultrasound scan showing extensive haemorrhage in both lateral ventricles with parenchymal extension on the left side. There is an echodense triangular lesion in the right periventricular area, which developed some time after the initial haemorrhage.*

PVL. Fifty two babies (26%) showed parenchymal lesions thought not to be primarily haemorrhagic. Eight babies died in the precystic phase of PVL, and in a further 19 infants cysts subsequently developed. In another 25 there was prolonged flare of periventricular echodensity.

A total of 123 infants had evidence of haemorrhage, cystic or precystic PVL, or flare (Fig. 6). Haemorrhage alone occurred in 71 infants, and a further 36 had the appearances of PVL together with haemorrhage. Fifty five infants had parenchymal involvement (Fig. 7), and only three of these showed the appearances of haemorrhage alone. Two others had PVL alone and 14 had a flare with no other abnormality. Thirty six of the 55 (65%) showed evidence of both haemorrhage and PVL.

Ventricular dilatation. Twenty one babies (10%) developed ventricular dilatation; nine were non-progressive and 12 required treatment. Twelve of the 21 (57%) had associated parenchymal involvement. Thirteen infants developed ventricular dilatation by 14 days, and in all cases it had developed by the age of 4 weeks.

Deaths. Forty two babies (21%) died, and all deaths occurred before discharge from hospital. Twenty one of the babies who died weighed ≤1000 g at birth. Fourteen of the deaths involved babies of 26 weeks' gestation or less. The time of death ranged from day 1 to 121, and 22 of the babies died before 1 week of age. Postmortem information was obtained in 30 of the 42 (71%) dead infants and is discussed in a paper on pathological correlation.[17]

Timing. Haemorrhage occurred within the first seven days of life in 83 of the 107 (78%) infants, but 17 infants (15%) showed the first ultrasound appearance of haemorrhage after 2 weeks of age. Nine of the 107 (8%) babies with haemorrhage did not show an abnormality until after 31 days of age.

The echodense phase of PVL was first noted by the age of 3 days in 14 babies and by 1 week in a further 11. In the final two infants the change was observed by the 10th day.

Nineteen infants developed cysts. One was present at the first scan at age 2 days. Cysts developed between 4 and 7 days in four and after 11 days in the rest. The median time for cysts to be first detected was 18 days of age. Only one infant developed an echofree cystic lesion after 30 days of age.

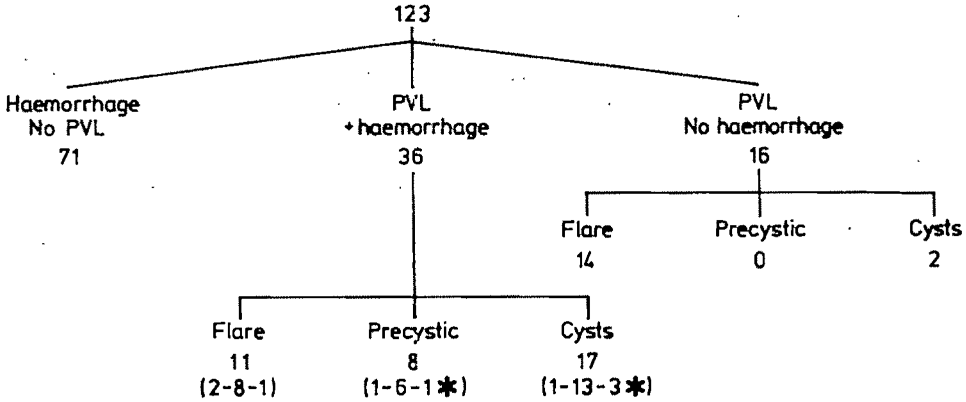

Fig. 6 *Distribution of haemorrhage and periventricular leucomalacia. Figures in brackets refers to the numbers of infants with germinal matrix, intraventricular, and parenchymal haemorrhage, respectively.*

*Four babies extension one side, periventricular leucomalacia the other.

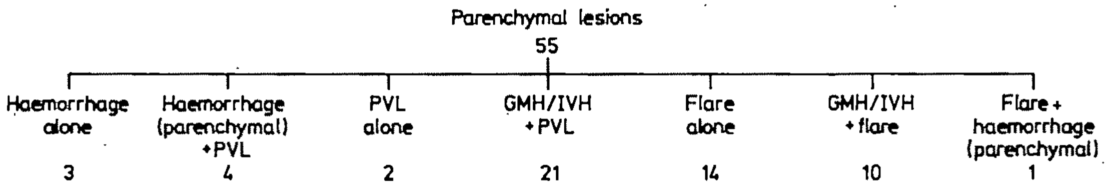

Fig. 7 *The patterns of parenchymal lesions. GMH=Germinal matrix haemorrhage; IVH=intraventricular haemorrhage; PVL=periventricular leucomalacia.*

Eleven of the 25 (44%) infants with prolonged flares were found to have this abnormality on the first scan (1–3 days). Eighteen (72%) developed flaring by the end of the first week. The flare was first noted after 20 days in only two infants.

Gestation. Of the 107 babies with haemorrhage, 99 (93%) were of 30 weeks' gestation or less. There was a pronounced decrease in the prevalence of haemorrhage from 62% at 30 weeks' to 19% at 31 weeks' gestation. A similar pattern was seen in the babies with PVL and prolonged flare: 25 out of 27 babies with PVL and 22 out of 25 babies with prolonged flare had a gestation of 30 weeks or less.

Discussion

The incidence of the ultrasound appearances that we believe represent cystic and precystic PVL is 13·5% in a group of very low birthweight infants. A previous retrospective study from the Hammersmith Hospital reported an incidence of 7·5%[4] and Fawer *et al* found the incidence to be 16·8% among relatively few infants of 34 weeks' gestation or below.[5] Bozynski and colleagues found cystic PVL in 5% of babies of birth weight ≤1200 g.[14] They studied only surviving infants and this is therefore not an accurate reflection of the overall incidence of the condition. Sinha and colleagues have recently reported the incidence of haemorrhage and ischaemia in a group of premature infants of 32 weeks' gestation or below.[11] Almost 18% of their infants showed ultrasound appearances of PVL. The only other published incidence of PVL derives from postmortem studies and varies between 7%[18] and 34%.[19] The latter study looked only at a highly selected group of 106 infants of birth weight ≤1500 g, all of whom were outborn. Computed tomography has proved to be disappointing in its ability to diagnose hypoxic-ischaemic lesions in the premature neonate[20 21] and compares poorly with real time ultrasound.

All areas of extensive echodensity within the parenchyma seen in association with intraventricular haemorrhage have until recently been assumed to be parenchymal haemorrhage. Hill *et al* were the first to recognise that parenchymal echodensity might be due to haemorrhagic infarction,[3] and Levene and colleagues later reported the evolution of 'haemorrhagic' PVL to cystic degeneration.[4] Nwaesei and coworkers have shown that echodensity may be due to gliosis without haemorrhage.[9] Few would now disagree that multiple small echolucent areas in the periventricular white matter represent PVL. A characteristic triangular echodense region in the parenchyma precedes cystic degeneration, and if seen in those infants who died before cysts develop then we have termed this the 'precystic' phase of PVL. Rushton reports accurate pathological correlation of PVL in five infants with the precystic ultrasound appearance,[8] and we have confirmed this.[17]

The most difficult and controversial area of the diagnosis of parenchymal lesions is the differentiation between extension of haemorrhage and PVL. Even at autopsy it may be impossible to distinguish primary haemorrhage from bleeding into an ischaemic lesion or venous infarction. Armstrong and Norman showed bleeding into an ischaemic periventricular area in 25% of their cases.[18] Flodmark and colleagues reported that of 19 preterm babies thought to have parenchymal haemorrhage on computed tomography, autopsy revealed bleeding into an ischaemic area in 18 (95%).[21] More recently Volpe and his colleagues, using positron emission tomography, showed extensive areas of diminished cerebral blood flow around an apparent primary parenchymal haemorrhage and suggested that the haemorrhage may have been secondary to ischaemia.[22] These reports do not prove that ischaemia is the underlying cause of parenchymal haemorrhage in all cases (as suggested by Rushton and colleagues), but they do make it likely that a number of such lesions are primarily ischaemic.

The appearance we refer to as 'parenchymal haemorrhage' and the subsequent evolution to porencephaly is quite different from that which we recognise as PVL (see Figs. 1 and 2). We have seen four infants in whom the appearance of parenchymal haemorrhage preceded contralateral PVL, and the two survivors developed porencephaly in one hemisphere and multiple cystic degeneration in the other. The aetiology of the underlying cause of these two lesions is, we believe, quite different. The timing also suggests that at least in some cases the massive parenchymal haemorrhage may induce secondary cerebral ischaemia with contralateral PVL. The delayed timing of the parenchymal echodensity after intraventricular haemorrhage also suggests venous infarction as the possible cause. Only eight infants showed the appearance we believe to represent parenchymal haemorrhage.

The term PVL was originally coined by Banker and Larroche to describe a specific but subtle macroscopic appearance in infants dying after a complicated perinatal course.[23] The most obvious lesions were 'white spots'. Since then the term PVL has been used more widely to describe a number of different macroscopic and microscopic appearances.[24 25] Although the aetiology of PVL may be border zone infarction, more than one aetiological factor is probably involved. We believe that some cases may be due to venous infarction: eight babies in our series showed a pattern of thrombus distending a lateral ventricle associated with development of a triangular echogenic area in the ipsilateral parenchyma. Pape and Wigglesworth have described congestion of the branches of the terminal vein in cases of massive germinal matrix haemorrhage with associated venous infarction of the surrounding periventricular white matter.[24] This would account for the incidence of PVL in infants with grade II haemorrhage.

Our overall incidence of haemorrhage (53%) corresponds with previous studies of the very low birthweight infant.[15] Of the 107 babies with haemorrhage described here, parenchymal extension occurred in only eight (7%), whereas previous workers have reported parenchymal involvement in about 20% of cases.[15] We believe that many parenchymal lesions that we now recognise as PVL have been classified as parenchymal haemorrhages in the past, and this would explain our lower incidence for the parenchymal lesion.

This is the first prospective study of the incidence of abnormal ultrasound appearances that have been carefully defined before starting collection of data. The definition of cystic and precystic PVL was based on sound pathological correlation, but we chose to use the term 'flare' to avoid assuming pathological abnormality in all cases where this was prolonged. Some periventricular echodensity is very common[26] and usually transient, and we elected to include as abnormal only those patients in whom the echoes persisted for two weeks or more and could be consistently seen in two planes. Our subsequent autopsy correlation with prolonged flares in three hemispheres confirmed extensive gliosis and microcalcification[17] and agrees with the data of Nwaesei *et al.*[9] Prolonged flare was seen in 12% of infants in our study and is clearly an important ultrasound finding, but we must await follow up data on the outcome of these infants before establishing its prognostic importance.

Previous studies have shown that most intraventricular haemorrhages occur within three days of birth.[15 27] In this study accurate timing of intraventricular haemorrhage was not possible, but 78% of the haemorrhages were noted before 7 days of age. Nine of the 107 haemorrhages (8%) occurred after 1 month of age. In one case the haemorrhage was first noted the day after a cardiac arrest, but in the other eight there was no preceding insult. This group resembles the pattern of late haemorrhages as reported by Hecht *et al*,[28] and like his cases the haemorrhages in our babies were small. The echodense phase of PVL was observed by 3 days of age in 14 cases and by 10 days of age in the other 13. This contrasts with the study of the Toronto group in which the mean age for first noting the echodensity was 37 days (range 1–85).[9] The difference may be partly due to their selection criteria as the babies had to survive at least 20 days for inclusion in their retrospective study.

In conclusion, we report an incidence of periventricular leucomalacia, precystic and cystic, of 13·5% in a cohort of 200 babies of birth weight ≤1500 g. The appearance of a prolonged flare, which we argue also represents PVL, occurred in a further 25 infants (12·5%). Overall, the ultrasound appearances of PVL when prolonged flares are included in this group occurred in 52 of the 200 infants, representing an incidence of 26% of very low birthweight infants. This is considerably higher than any previous report.

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Intraventricular haemorrhage and periventricular leucomalacia: ultrasound and autopsy correlation

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SUMMARY The brains of 30 infants who died after at least one real time ultrasound scan were examined after fixation. The ultrasound diagnosis of either periventricular haemorrhage or periventricular leucomalacia was compared with the macroscopic and histological appearances. Each hemisphere was considered separately for both periventricular haemorrhage and periventricular leucomalacia. The accuracy of ultrasound diagnosis for periventricular haemorrhage was 88%, with sensitivity of 91% and specificity of 85%. The accuracy for periventricular leucomalacia was 90%, with sensitivity of 85% and specificity of 93%. Ultrasound was shown to diagnose the entire range of periventricular leucomalacia lesions. Three hemispheres showed the appearance of prolonged flare, and this correlated with extensive spongiosis and microcalcification of the periventricular white matter, although no macroscopic lesion was seen.

There is now clear evidence that the long term neurodevelopmental prognosis for neonates with intraventricular haemorrhage is significantly better than for those with periventricular leucomalacia (PVL).[1-3] If ultrasound imaging is to be effective in predicting prognosis then clearly an accurate differentiation of the pathological entities must be possible on scanning. Previous workers have reported accurate correlation between ultrasound demonstration of intraventricular haemorrhage and its finding on computed tomography or at autopsy,[4-9] but in none of these studies was an attempt made to differentiate parenchymal lesions due to 'extension of haemorrhage' from PVL. As part of a prospective study of intraventricular haemorrhage and PVL in the preterm neonate we have had the opportunity to correlate ultrasound scan and autopsy findings and we now report our results.

Patients and methods

Over a 16 month period (1 January 1984 to 30 April 1985) 200 neonates of birth weight ≤1500 g admitted to two neonatal intensive care units (Leicester Royal Infirmary and Nottingham City Hospital) had regular cranial ultrasound scans. At least one scan had to have been performed during life for the patient to be included in the study. In both centres an ATL Mark III real time sector scanner fitted with a 3·5, 5, and 7·5 MHz multifrequency scanhead was used. Ultrasound diagnoses based on our previous definitions[10] were made before autopsy in all cases. The brain was removed complete at the time of postmortem examination and suspended in 10% formalin for at least one month before sectioning. Coronal cuts were made at 1 cm intervals and the macroscopic appearances noted. Histological examination of the periventricular area was performed in most cases. For the purposes of analysis, each hemisphere was considered separately. The number of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) ultrasound diagnoses for each cerebral hemisphere was tabulated. The accuracy of ultrasound was measured by calculating TP+TN/total number of hemispheres examined. Sensitivity was calculated as TP/(TP+FN) and specificity as TN/(FP+TN).

To show the range of PVL lesions we have included five additional babies who were not included in our previous study.[10] Two of these had scans performed soon after death but had no in vivo scan, and a further two preterm infants had birth weights that had excluded them from the previous study. The final infant was born at 29 weeks' gestation and suffered severe arrhythmias in the first 24 hours of life related to hyperkalaemia. An ultrasound scan at the age of 17 days showed extensive bilateral cystic PVL, involving temporal and occipital regions, and this was still present when she was last scanned at the age of 7 weeks. She died suddenly aged 6 months and thus illustrates the more long term evolution of PVL.

Results

Forty two of the 200 study babies died, and all deaths occurred before discharge from hospital. Postmortem examination was performed in 31 of the 43 deaths, but in one infant the brain was too soft to fix. The results of the correlation between autopsy and ultrasound examinations are shown in Tables 1 and 2 for the 30 infants with complete postmortem data. Histological examination was performed on 25 brains.

Haemorrhage. Haemorrhage into the germinal matrix or ventricle or extension into the cerebral parenchyma was diagnosed both by ultrasound and subsequently at autopsy in 31 hemispheres. The results are summarised in Table 1. A false positive ultrasound diagnosis of haemorrhage was made in four hemispheres (three infants) in which postmortem examination subsequently showed a normal hemisphere. In three the ultrasound appearance was thought to consist of haemorrhage in the region of the germinal matrix, and the other seemed to show the appearances of more extensive clot in the lateral ventricles. A false negative diagnosis of haemorrhage was made in three hemispheres (two babies) (Table 2). All three hemispheres contained a small germinal matrix haemorrhage that had ruptured into the ventricles. The accuracy of ultrasound diagnosis of haemorrhage was 88%. The sensitivity of diagnosis was 91% and specificity 85%.

Table 1 *Correlation between ultrasound and postmortem diagnoses for the study group of 60 hemispheres. As each hemisphere may have more than one form of disease the numbers do not add up to 60. Values are No (%)*

Ultrasound observations	*Postmortem observations*		
	Normal	*PVH*	*PVL*
Normal	22 (78)	3 (11)	3 (11)
PVH	4 (11)	31 (89)	0
PVL	3 (15)	0	17 (85)

PVH=Periventricular haemorrhage; PVL=periventricular leucomalacia.

Table 2 *Correlation between postmortem and ultrasound diagnoses for the 60 hemispheres. Values are No (%)*

Postmortem observations	*Ultrasound observations*		
	Normal	*PVH*	*PVL*
Normal	22 (76)	5 (17)	2 (7)
PVH	3 (9)	31 (91)	0
PVL	3 (15)	0	17 (85)

PVH=Periventricular haemorrhage; PVL=periventricular leucomalacia.

Ischaemic lesions. Echodensity in the periventricular white matter detected by ultrasound and thought not to be parenchymal extension of periventricular haemorrhage was seen in 20 hemispheres, and PVL lesions were diagnosed at autopsy in 20 hemispheres (Tables 1 and 2). The accuracy of the ultrasound diagnosis was 90%. A false positive ultrasound diagnosis of abnormal periventricular echodensity was made in three hemispheres (two infants). One child was only scanned once and the other had three scans, and mild bilateral flare was thought to be present on each occasion. A false negative ultrasound diagnosis of PVL was made in three hemispheres (two infants). In two hemispheres there was non-haemorrhagic PVL and in one hemisphere extensive haemorrhagic PVL was found and not previously detected by ultrasound. The sensitivity of ultrasound in the diagnosis of PVL was 85% and specificity 93%.

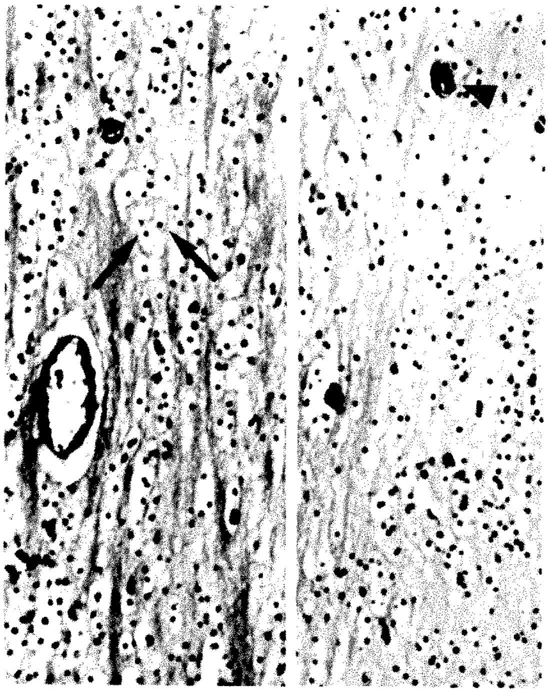

Fig. 1 *Spongiosis and microcalcification in an infant with prolonged flare. Haematoxylin and eosin stain, showing generalised spongiosis of periventricular white matter (arrow) and microcalcification (arrow head).*

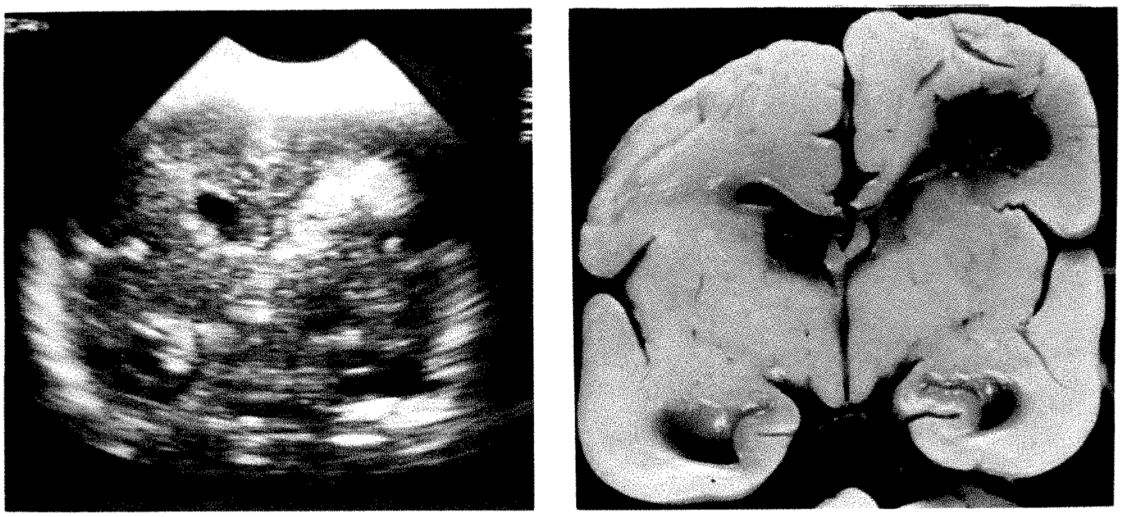

Fig. 2 *Precystic periventricular leucomalacia. Coronal ultrasound view (left) showing triangular shaped echodensity in the right hemisphere. The pathological correlate (right) confirms haemorrhagic infarction in the region of the echodensity. There is a small unruptured subependymal haemorrhage on the right side and a somewhat larger lesion involving the left subependymal region.*

Range of PVL lesions. To show the variety of PVL lesions an additional five infants have been considered together with the study infants. The ultrasound appearances we have described as prolonged flare[10] occurred in two infants (three hemispheres) whose brains were examined at autopsy. The flares persisted for two weeks and three months, respectively, and were present on the last scan before death. No macroscopic abnormality was seen in either brain, but on histological examination extensive spongiosis and microcalcification was present in the periventricular white matter corresponding to the areas of echodensity (Fig. 1).

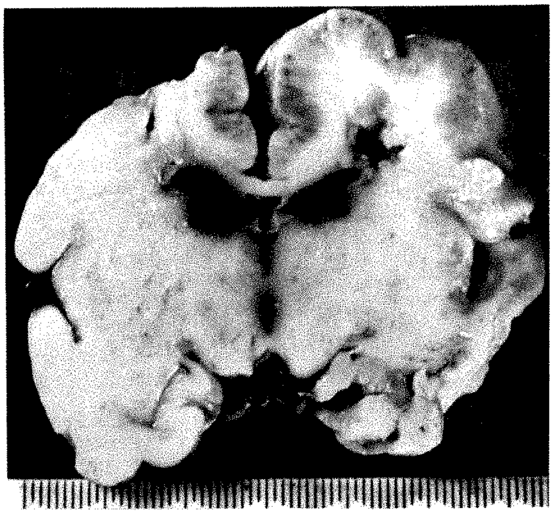

Fig. 3 *Cystic periventricular leucomalacia, showing a single cavity in the right periventricular region separate from the lateral ventricle. Intraventricular clot is also present arising from bilateral subependymal haemorrhages.*

At autopsy one infant showed the characteristic 'white spots' described by Banker and Larroche.[11] On ultrasound examination persistent bilateral flare was noted and it was thought that small echofree cavitations subsequently occurred shortly before death. The cysts were not confirmed at autopsy, but the echofree areas may have corresponded to the macroscopic white spots of lipid accumulation.

Seven infants (eight hemispheres) showed the pathological appearance of haemorrhagic infarction at autopsy. These infants died between the ages of 5 hours and 13 days. In all cases the floor of the ventricle appeared intact. In six of these infants in whom an ultrasound diagnosis of precystic PVL was made the necropsy appearance was consistent with haemorrhagic infarction in the region of the echodensity (Fig. 2).

Three infants were found to have periventricular cysts at autopsy. In all cases the initial ultrasound appearance was of a triangular shaped echodensity with its apex towards the angle of the lateral ventricle, from which echofree cavities developed in two of the three cases. A unilateral periventricular cyst was not detected in one baby on scanning,

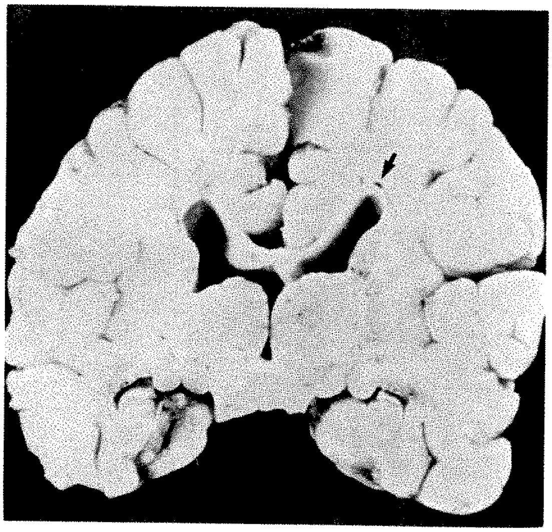

Fig. 4 *Resolving cavities. Coronal section from an infant shown to have extensive cystic periventricular leucomalacia in the newborn period. Autopsy shows a collapsed cavity in the right periventricular region (arrowed). There is also compensatory ventricular enlargement.*

although a flare had been seen in the corresponding area. This infant was scanned only once during life (Fig. 3).

One infant died aged 6 months of sudden infant death syndrome who at discharge from the neonatal unit showed extensive echofree cavitation in the periventricular white matter of both hemispheres. At autopsy there was irregular, ventricular dilatation, but the posteriorly placed cysts remained only as flattened cavities (Fig. 4), while the anterior cysts could no longer be seen at all.

Discussion

We have shown that real time ultrasound is an extremely good method for diagnosing both intraventricular haemorrhage (accuracy 88%) and PVL (accuracy 90%) in a series of 30 brains. Previous studies have produced similar autopsy correlation with the ultrasound diagnosis of periventricular haemorrhage in the region of 90% accuracy.[5-9] In the two infants we report here with a false negative diagnosis of haemorrhage there was an interval of a few hours between the last scan and death, and the bleeding may have occurred during this time. A false positive diagnosis of haemorrhage was made in four hemispheres (three babies), all of whom died within 24 hours of birth. One baby had a massive contralateral parenchymal haemorrhage, and it is possible that on scanning we detected spread of thrombus from this site with no actual focus of bleeding within the ventricle in question. Szymonowicz and her colleagues reported congestion of the germinal matrix region that simulated germinal matrix haemorrhage,[9] but this was not present in our infants.

Less information is available on the correlation between the ultrasound diagnosis of PVL and autopsy data. Nwaesei and colleagues reported 78% accuracy between ultrasound demonstration of increased echos or cysts in the periventricular region and the finding of PVL at autopsy in the corresponding site.[12] In addition, they made the important point that both haemorrhagic and non-haemorrhagic infarction may produce identical changes on ultrasound. More recently, Fawer *et al* reported excellent autopsy correlation in five infants with the ultrasound appearances of PVL (three non-cystic and two cystic), and there were no false negative diagnoses.[13] In our study ultrasound failed to detect PVL in two babies (three hemispheres). In one hemisphere the changes were early and in the other two there were histological abnormalities only (spongiosis and reactive astrocytosis but no microcalcification). A discrete cyst was missed in one infant whose only scan was performed 48 hours before his death aged 5 days. The scan showed some flaring in the area where the cyst was subsequently observed at postmortem examination. The cyst undoubtedly would have been present at the time of the scan, and we cannot explain why it was not detected, but distortion may possibly have occurred during fixation to give a cystic appearance larger than it may have been in vivo.

Armstrong and Norman reported bleeding into the ischaemic area in 25% of their infants with PVL,[14] and we found this in six of 34 (18%) hemispheres. There is, however, considerable controversy concerning the differentiation between parenchymal extension of intraventricular haemorrhage and bleeding into a previously ischaemic lesion. Rushton and colleagues have recently reported eight infants with parenchymal abnormalities on ultrasound and at autopsy all showed PVL.[15] These authors proposed that this is the underlying aetiology to all parenchymal haemorrhagic lesions. The evidence for this is still far from conclusive and it is beyond the scope of this study to resolve this question.

We have attempted to differentiate parenchymal extension of intraventricular haemorrhage from PVL by ultrasound scanning and report the relative incidence in a separate paper.[10] The autopsy data reported here confirm that all cases of haemorrhagic infarction diagnosed by ultrasound were subsequently found to be correct. No infant with parenchymal extension of intraventricular haemorrhage died in the acute stages and correlation in this group was not possible. We are encouraged, however, by the accuracy of ultrasound in diagnosing the range of PVL lesions reported here. This supports the validity of the ultrasound definitions that we have previously reported and used to evaluate prospectively a large group of very low birthweight infants.[10]

We have had the opportunity of observing a variety of appearances in the immature brain that represent the range of perinatal ischaemic injury. The histologic appearances of PVL have been described originally by Virchow in 1867[16] and later by Banker and Larroche.[11] These appearances may be present without macroscopic abnormality, and we have shown that ultrasound can show both gliosis and the 'white spots' of Banker and Larroche. Haemorrhagic infarction and subsequent cavitation is also readily diagnosed by ultrasound imaging. Two cases have been reported of infants showing extensive cavitation on sequential ultrasound scans in whom the echofree cystic lesions disappeared by 6 months.[17 18] We report here pathological correlation with this sequence of scan findings. With collapse of the cystic cavities, compensatory ventricular dilatation occurred due to cerebral atrophy. As far as we know this is the only such pathological correlation reported to date.

In conclusion, real time ultrasound scanning seems to be an excellent method for identifying the entire range of PVL lesions. It is of particular interest that apparently normal macroscopic brain appearances are echodense in the presence of microscopic calcification and gliosis. In addition, both the specificity and sensitivity of ultrasound is high for the diagnosis and exclusion of these lesions. We have confirmed that the ultrasound distinction between types of PVL as described elsewhere[10] is a realistic and reliable proposition.

We are grateful to the staff of the LRI and NCH neonatal units for their cooperation and to Dr Pippa Stocks for the collection of specimens. We thank Professor J S Wigglesworth for his opinion on the brain of the cot death infant.

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The metabolic load of stored blood. Implications for major transfusions in infants

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SUMMARY Plasma electrolyte, intermediary metabolite, and hormone concentrations were measured in samples of 110 units of citrate phosphate dextrose blood being used for clinical transfusions. The most important changes from the physiological range were in sodium, potassium, glucose, and lactate concentrations. Mean sodium concentrations fell from 170 mmol/l at the beginning of storage to 156 mmol/l at the end and mean potassium concentrations rose from 7 mmol/l to 25 mmol/l. Glucose had a mean concentration of 20 mmol/l at the beginning of storage and had only fallen to 15 mmol/l at the end. Mean lactate concentrations increased from 7 mmol/l at the beginning of storage to 25 mmol/l at the end. Many samples had cortisol, insulin, and growth hormone concentrations within the physiological range. Citrate phosphate dextrose blood contains a large substrate load that changes during storage and that should be taken into account when infants are transfused large volumes of blood. The strong correlation coefficients with duration of storage for sodium, potassium, and lactate (−0·71, 0·91, and 0·90, respectively) indicate that concentrations of these substrates can be predicted within a narrow range if the duration of blood storage is known.

Large quantities of stored blood may have to be transfused into very ill infants in a number of circumstances—for example, exchange transfusion, during and after surgery, or after acute haemorrhage. Stored blood contains metabolically active substrates and electrolytes, which may be poorly tolerated by sick infants if given in large quantities. A number of studies have illustrated the serious metabolic effects of individual substrates from transfused stored blood.[1-3] These effects may be modified, however, by other substrates present in abnormal quantities.

A more detailed knowledge of the substrate load of stored blood would enable potential metabolic disturbances to be accurately predicted when infants receive large blood transfusions. Furthermore, this information is essential for the interpretation of metabolic studies in critically ill infants.

Although there is some information on the substrate content of stored blood,[3-7] detailed quantitative data on the substrate load and the effects of storage are not available. This study was designed to measure the electrolyte, metabolite, and hormone content of stored blood in relation to duration of storage.

Methods

Aliquots of 10 ml were taken from each of 115 units of citrate phosphate dextrose stored blood being used for clinical transfusions. Samples were taken before the six hour expiry time at room temperature. Blood was available for transfusion from the second day after collection after the completion of virological screening for hepatitis antigens. Eighty one samples were taken from blood between two and eight days after collection, and the remainder of the samples were evenly distributed over the subsequent four weeks from collection.

Glucose, lactate, pyruvate, alanine, glycerol, and 3-hydroxybutyrate concentrations were measured in perchloric acid extracts of 0·5 ml whole stored blood by the method described by Lloyd and colleagues.[8] The remaining sample was centrifuged for five minutes and the separated plasma deep frozen for the subsequent batch analysis of electrolytes (routine laboratory autoanalyser (Astra or Chemispek)), total protein (Biuret method), and the hormones insulin,[9] cortisol,[10] and growth hormone (radioimmunoassay, supraregional assay laboratory, Newcastle upon Tyne).

As all the above samples were deep frozen before analysis it was necessary to obtain further samples for the measurement of osmolality. Plasma samples were obtained, therefore, from a further 11 units of stored blood within a week of collection after five minutes of centrifugation. Osmotic activity was measured in these samples immediately by the method of freezing point depression, using an Advanced Instruments Micro Osmometer model 3MO.

Statistics. Statistical analyses were performed, using SPSS and SAS statistical packages on an Amdahl mainframe computer. Linear correlation and *t* test procedures were used as appropriate.

Results

Results of the various assays for the whole period of blood storage are summarised in the Table, which shows correlation coefficients, p values, and normal paediatric ranges.

Sodium. During the period of storage, mean sodium concentrations fell from 170 mmol/l to 156 mmol/l (170 to 156 mEq/l at 35 days (r=−0·71, p<0·001) (Fig. 1). In the 81 samples obtained between two and eight days from collection sodium concentration was in the range of 162–182 mmol/l, with a mean (SD) of 170 (5·0) mmol/l.

Potassium. During the period of storage, mean potassium concentrations increased from 7·0 mmol/l to 25·0 mmol/l (7·0 to 25·0 mEq/l) in the last week of storage (r=0·91, p<0·001) (Fig. 2). Between two and eight days from collection, the mean (SD) potassium concentration was 8·6 (2·0) mmol/l, with a range of 5·5–15·3 mmol/l. Thus the potassium concentration had already reached the upper limit of the physiological range by the second day of storage.

Calcium and magnesium. Both stored blood calcium concentrations (mean (SD) 2·3 (0·4) mmol/l, (9·2 (1·6) mg/100 ml), range 1·8–3·7 mmol/l) and magnesium concentrations (mean (SD) 0·8 (0·2) mmol/l (1·9 (0·5) mg/100 ml), range 0·6–2·0 mmol/l) increased gradually during the period of blood storage (r=0·53, p<0·001, and r=0·33, p<0·001, respectively). There was a very wide scatter,

Table *Results of assays of electrolyte, metabolite, and hormone concentrations of stored blood*

Index	*No of samples*	*Mean (SD) concentration (mmol/l*)*	*Range (mmol/l*)*	*Normal Paediatric range (mmol/l*)*	*Correlation with duration of storage*	*p Value*
Sodium	115	168 (6)	155 – 182	136 – 145	−0·71	<0·001
Potassium	115	11·0 (4·6)	5·5 – 24·6	3·5 – 5·6	0·91	<0·001
Chloride	115	78 (3)	69 – 86	98 – 106	−0·31	<0·001
Calcium	114	2·3 (0·4)	1·8 – 3·7	2·2 – 2·75	0·53	<0·001
Magnesium	114	0·8 (0·2)	0·6 – 2·0	0·6 – 0·95	0·33	<0·001
Total carbon dioxide	115	11·1 (2·8)	4·0 – 19	18 – 25	−0·25	<0·01
Creatinine (μmol/l)	114	91 (14)	59 – 141	35 – 106	−0·04	NS
Urea	115	4·6 (1·2)	1·3 – 8·2	2·5 – 6·6	0·01	NS
Total protein (g/l)	112	59·4 (4·7)	50 – 70	64 – 75	0·17	<0·05
Albumin (g/l)	49	38·7 (3·3)	31 – 45	37 – 50	0·3	<0·05
Glucose	115	19·2 (3·7)	8·4 – 31·4	3·3 – 5·5 (Non-fasting)	−0·49	<0·01
Lactate	115	10·5 (4·6)	3·3 – 23·3	0·4 – 1·19	0·9	<0·001
Pyruvate	114	0·24 (0·10)	0·01 – 0·57	0·03 – 0·16	−0·37	<0·001
Alanine	114	0·38 (0·10)	0·02 – 0·68	0·18 – 0·48	0·31	<0.001
Glycerol	113	0·05 (0·02)	0·01 – 0·15	0·03 – 0·10	−0·03	NS
3-Hydroxybutyrate	109	0·04 (0·04)	0·01 – 0·26	0·01 – 0·34	−0·04	NS
Non-esterified fatty acids	104	0·65 (0·22)	0·25 – 1·54	0·2 – 1·45	0·22	<0·01
Insulin (mU/l)	114	†12·2	<1·0 – 33·4	5·0 – 40 (Fasting)	0·13	NS
Cortisol (nmol/l)	111	†301	62 – 906	200 – 700 (0800h)	0·03	NS
Growth hormone (mU/l)	110	†3·2	0·1 – 62·3	<12 (Unstressed)	−0·14	<0·1
Osmolality (mOsm/kg)	11	314 (4)	308 – 320	270 – 290		

*Unless otherwise stated.
†Non-Gaussian distribution.
NS=Not significant.

Conversion: SI to traditional units—Sodium: 1 mmol/l=1 mEq/l; potassium: 1 mmol/l=1 mEq/l; chloride: 1 mmol/l=1 mEq/l; calcium: 1 mmol/l=4 mg/100 ml; magnesium: 1 mmol/l≈2·4 mg/100 ml; total carbon dioxide: 1 mmol/l=1 mEq/l; creatinine: 1 μmol/l≈0·01 mg/100 ml; urea: 1 mmol/l≈5·9 mg/100 ml; total protein: 1 g/l=0·1 g/100 ml; glucose: 1mmol/l≈18 mg/100 ml; lactate: 1 mmol/l=9 mg/100 ml; pyruvate: 1 μmol/l≈0·009 μg/100ml; alanine: 1 mmol/l=1 mEq/l; glycerol: 1 mmol/l=1 mEq/l; 3-hydroxybutyrate: 1 mmol/l=1 mEq/l; non-esterified fatty acids: 1 mmol/l=1 mEq/l; insulin: 1 mU/l=1 μU/ml; cortisol: 1 mmol/l≈0·04 μg/100 ml; growth hormone: 1 mU/l≈0·4 ng/ml.

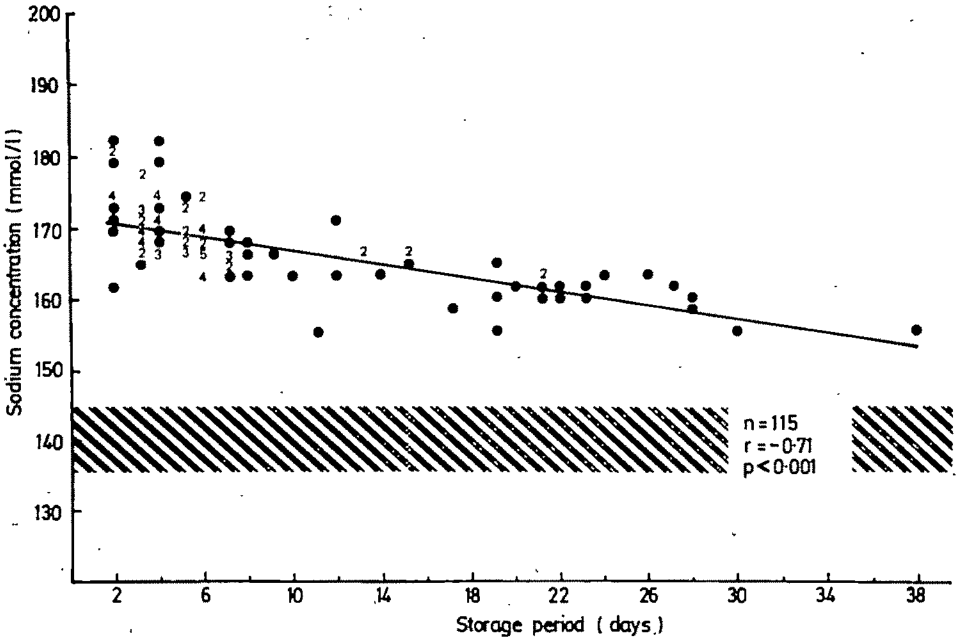

Fig. 1 *Results of assays of sodium concentrations for whole period of blood storage. Hatched area represents the normal range.*

Conversion: SI to traditional units—Sodium: 1 mmol/l=1 mEq/l.

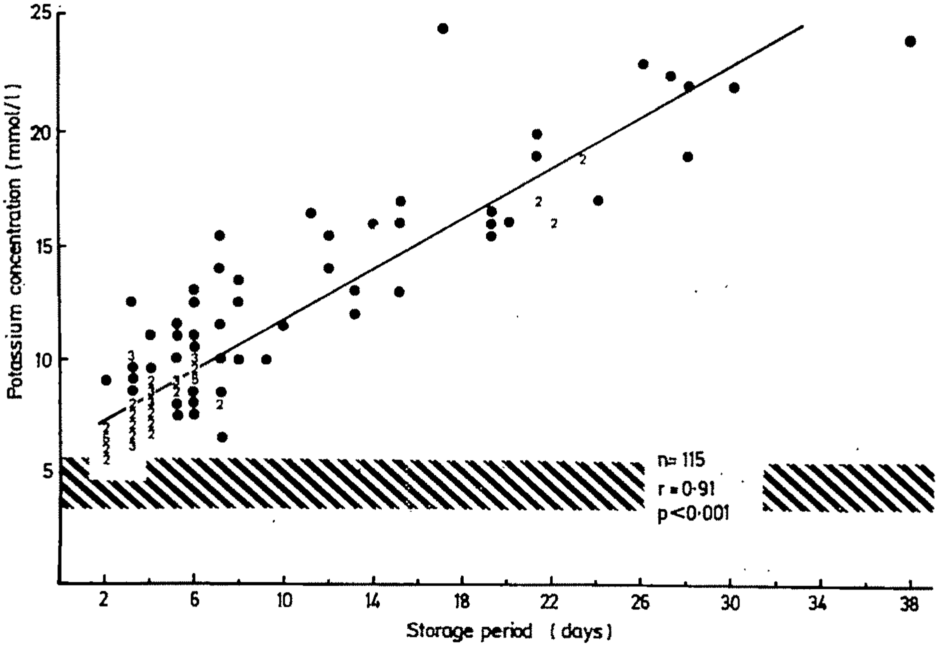

Fig. 2 *Results of assays of potassium concentration for whole period of blood storage. Hatched area represents the normal range.*

Conversion: SI to traditional units—Potassium: 1 mmol/l=1 mEq/l.

however, for both calcium and magnesium throughout storage.

Total protein and albumin. Both total protein concentrations (n=112), mean (SD) 59·4 (4·7) g/l and range 50–70 g/l, and albumin concentrations (n=49), mean (SD) 38·7 (3·3) g/l and range 31–45 g/l, increased slightly during storage (r=0·17, p<0·05, and r=0·3, p<0·05, respectively).

Glucose. The glucose concentrations of all units of citrate phosphate dextrose stored blood were markedly above the normal non-fasting range throughout the period of storage (Fig. 3). There was a significant fall in glucose concentration during storage from around 20 to 15 mmol/l (360–270 mg/100 ml) (r=−0·49, p<0·001). (Fig. 3). Between the second and eighth days of storage, mean (SD) glucose concentrations were 19·2 (3·5), mmol/l (n=81), with a range of 8·4–31·4 mmol/l.

Lactate. Lactate concentrations rose significantly from around 7 mmol/l (63 mg/100 ml) at the beginning of storage to around 25 mmol/l at the end of storage (r=0·9, p<0·001) (Fig. 4). From the second up to the eighth day from collection, mean (SD) lactate concentrations were 7·8 (1·8) mmol/l, with a range of 3·3–14·3 mmol/l.

Pyruvate. Pyruvate concentrations in stored blood were widely scattered during the first week of storage, with a mean (SD) of 260 (110) µmol/l (2·3 (1·0) mg/100 ml) and a range of 10–570 µmol/l. There was a slight but significant fall in pyruvate concentrations during the storage period (r=−0·37, p<0·001).

Alanine. Stored blood alanine concentrations also showed a wide scatter during storage, with a mean of 0·38 (0·10) mmol/l (0·38 (0·10) mEq/l) and a range of 0·02–0·68 mmol/l, but did increase slightly during storage (r=0·31, p<0·001).

Insulin, cortisol, and growth hormone. Neither insulin nor cortisol were totally degraded in stored blood and both showed appreciable concentrations throughout the period of storage. The mean insulin concentration was 12·2 mU/l, with a range of <1–33·4 mU/l, and mean cortisol concentration was 301 nmol/l (10·9 µg/100 ml), with a range of 62–906

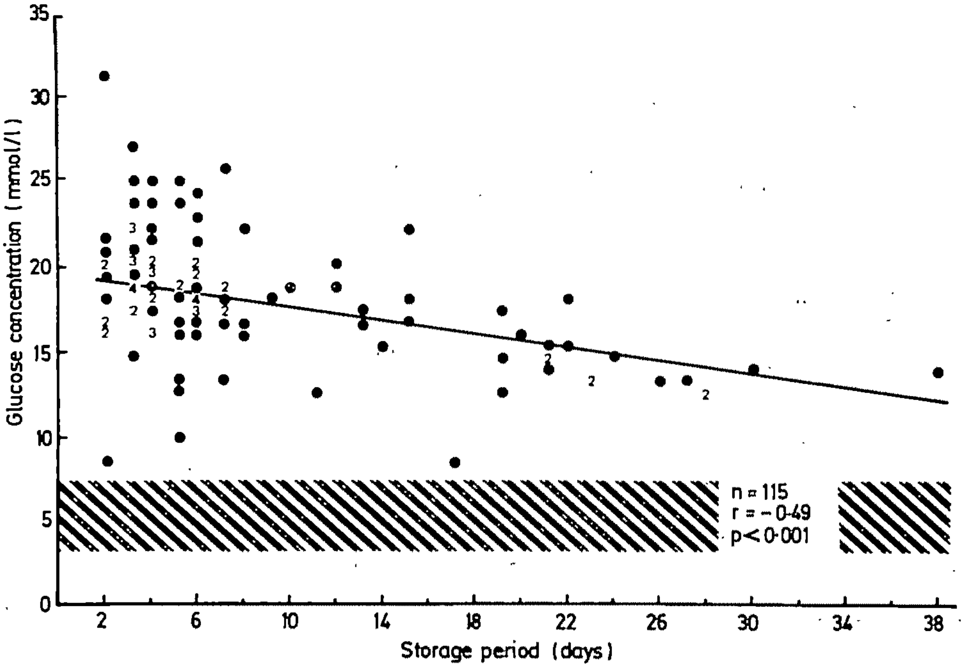

Fig. 3 *Results of assays of glucose concentrations for whole period of blood storage. Hatched area represents normal range.*

Conversion: SI to traditional units—Glucose: 1 mmol/l≈18 mg/100 ml.

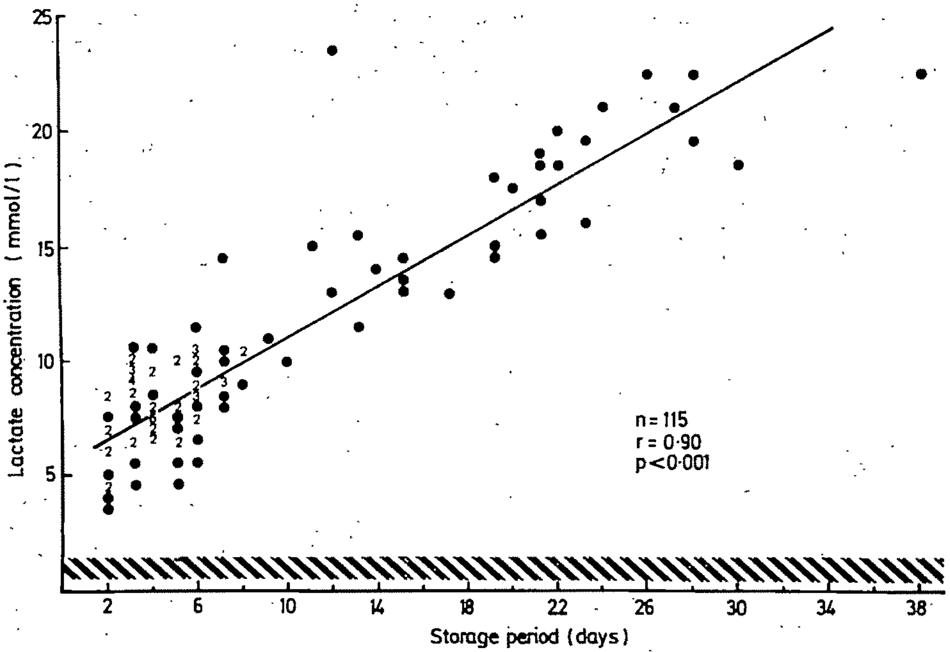

Fig. 4 *Results of assays of lactate concentrations for whole period of blood storage. Hatched area represents normal range.*

Conversion: SI to traditional units—Lactate: 1 mmol/l=9 mg/100 ml.

nmol/l. These concentrations were not significantly correlated with duration of storage. The mean growth hormone concentration was 3·2 mU/l, with a range of 0·1–62·3 mU/l. Concentrations were not correlated with the age of blood.

Osmolality. The osmolality of all the 11 units of blood less than one week old analysed was above the upper limit of the physiological range (290 mOsm/kg). The mean (SD) osmolality in the samples was 314 (4)mOsm/kg, with a range of 308–320 mOsm/kg.

Discussion

The electrolyte and substrate content of stored blood is derived from the addition of:

(i) citrate phosphate dextrose adenine anticoagulant preservative solution;

(ii) the metabolism of stored blood cells;

(iii) the volume and plasma constituents of the donor blood.

The anticoagulant preservative solution increases both the sodium and glucose concentrations of stored blood by roughly 20 mmol/l.

Even during storage at 4°C, red cell metabolism continues anaerobically and lactate is produced by glycolysis.

The data presented in this study show that citrate phosphate dextrose stored blood contains a large substrate load, which alters during storage. Further, it is possible to predict accurately the sodium, potassium, glucose, and lactate load of a given unit of blood if the duration of storage is known.

What are the implications of these findings? The clinical situations of exchange transfusion in the neonate and transfusion after surgery and haemorrhagic shock can be used to illustrate some of the important metabolic effects.

Hypernatraemia. Citrate phosphate dextrose blood within the first week of collection is used for exchange transfusions. From the data presented in this paper, therefore, the mean (SD) sodium concentration of the donor blood will be 170 (5) mmol/l. After an exchange transfusion 85–90% of the blood volume may be derived from stored blood. The osmolality of the stored blood plasma is higher than that of normal plasma (see above) and will cause considerable water and electrolyte flux. The plasma sodium concentration will rapidly increase to hypernatraemic concentrations, with its accompanying dangers.[11]

Hypernatraemia has been documented as a 'transient phenomenon' after exchange transfusions[12] and is more common in infants of low birth weight.[13] This transient phenomenon cannot be related to rapid excretion, as even full term healthy neonates cannot rapidly excrete a sodium load.[14] It is probable that this excess sodium will be distributed throughout the extracellular space, thus expanding it at the expense of intracellular water.

These changes in intracellular water will also result in a reduction of brain cell volume, may cause overall shrinkage of the brain, and may result in low intracranial pressure, causing capillary dilatation and subsequent vessel rupture. Exchange transfusion is a known aetiological factor in neonatal cerebral haemorrhage.[15]

Hyperkalaemia. Hyperkalaemia sufficient to induce serious cardiac arrhythmias has been described during exchange transfusions.[3] Our data show a significant rise of potassium concentration during the first week of storage, which is related to a pronounced reduction in the activity of cell membrane Na^+/K^+ adenosine triphosphatase during storage at 4°C.[16] As a result, sodium and potassium are pumped back against their concentration gradients more slowly than the rate of passive diffusion.

Hyperglycaemia. The glucose load of all citrate phosphate dextrose stored blood has a mean concentration of 19·2 mmol/l. Thus a rapid large volume exchange transfusion may induce severe hyperglycaemia.[17] Hyperglycaemia is known to interfere with platelet function[18] and is now known to affect adversely neurological recovery from cerebral ischaemia.[19] Less mature infants respond to a glucose stimulus with a lower insulin output whose peak concentration may occur up to two hours later, thus making them susceptible to the development of rebound *hypo*glycaemia.[17]

Hyperglycaemia unrelated to infusion of glucose has been described in infants with hypernatraemia whose insulin responses were inappropriately low.[20 21] Insulin facilitates active transport of glucose into brain cells,[22 23] but in those clinical circumstances glucose would be an extracellular obligate osmole and, therefore, along with sodium, increase the cellular dehydration.

The metabolic stress response to surgery and haemorrhagic shock with the associated increase in glucagon, catecholamine, and cortisol concentrations[24] may modify the handling of the substrate load of blood transfused during the perioperative period. In contrast to these hormones that stimulate gluconeogenesis,[25] insulin secretion is suppressed during surgical stress, and cellular glucose uptake is consequently reduced. In these clinical circumstances lactate is also used for gluconeogenesis.

Anaerobic metabolism secondary to poor tissue perfusion in haemorrhagic shock produces lactic acidaemia. The transfusion of stored blood with a raised lactate concentration, mean concentration of 8·0 mmol/l during the first week of storage, will accentuate the metabolic acidosis.

Conclusions

The use of very recently stored citrate phosphate dextrose blood does *not* prevent the administration of large sodium and glucose loads. The effect of each of these substrates may increase the adverse effects of the other, particularly in relation to neurological damage. Potassium and lactate concentrations rise rapidly, and, even within the first week of blood storage, may have produced concentrations considerably above the physiological range.

The changes in concentration of other electrolytes and intermediary metabolites illustrate the alteration in red cell permeability and continuing metabolism during blood storage. These results and the preservation of some hormones in stored blood are important considerations in metabolic studies carried out in infants.

The good correlation coefficients with duration of storage for sodium, potassium, and lactate indicate that concentrations of these substrates can be predicted within a narrow range in a given unit of blood if the duration of storage is known.

These data would support the use of fresh blood collected in heparin for large volume transfusions both in infants who have short gestational ages and infants who are very ill to avoid these potential problems.

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British Paediatric Association

Annual meetings

At York University:
1987 April 7–10
1988 April 12–16
1989 April 11–15

At University of Warwick:
1990 April 3–7
1991 April 16–20
1992 April 7–11
1993 April 19–23 (provisional)
1994 April 11–15 (provisional)

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Infantile diarrhoea due to water complementation of breast and bottle feeding

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SUMMARY This study investigated the prevalence of unusual infant feeding practices among 204 mothers of infants aged 1–12 months, who were admitted with acute diarrhoea to the only two national hospitals in Kuwait. Ninety per cent of the mothers boiled water to prepare a powdered milk formula, but only 15% boiled water for drinking.

Thirty nine infants (19%) were admitted more than once. Better family state in terms of socioeconomic class, maternal education, and breast feeding gave some protection against re-admission, though this was not significant. It seems that the condition of drinking water is an important cause of diarrhoea and hence of re-admission. The number of re-admissions was twice as high among infants drinking unboiled (unfiltered or mineral) water than among those drinking boiled or unboiled but filtered water. Breast feeding is protective if no extra water is given.

Kuwait is a small country situated at the head of the Arabian Gulf with a population of 1·3 million and with 50 000 live births every year. The water supply in Kuwait is derived from distillation of sea water; some areas are supplied through pipes, others by water tankers. The water is usually muddy, and most houses have filters to clear it. Some families use mineral water, and at least 35 types are imported to Kuwait. In a recent study it was claimed that 55% of 'mineral water' imported to Qatar was tap water. (Kotb A. Personal communication.) Although many mothers prepare formula feeds with boiled, cooled water, they tend to give additional drinking water to the infants from any source.[1] In hot weather infants probably drink more water than breast milk or formula.

The aim of this study was to ascertain if there was an association between the types of water used and the frequency of admission due to acute infantile diarrhoea.

Patients and methods

A total of 204 mothers of infants aged 1–12 months were interviewed when their infants were admitted with acute diarrhoea to Al-Sabah and Al-Ameri Hospitals (the only two national hospitals in Kuwait), during four months between early March and the end of June 1981. The population studied was multi-national, comprising many Arab and Asian countries. The interviews (carried out by S P-S and two trained social workers) included details of: living area, referring clinic, birth place, age, sex, nationality, weight at birth, weight on admission, the mother's education and occupation, and father's social class (I, II, III, IV, or V, classified according to the general registrar classification of occupation for the United Kingdom).

Each mother was asked how she defined diarrhoea, the number of attacks of diarrhoea at home since the baby's birth, and the remedies used; the number of attendances at paediatric clinics because of diarrhoea; the number of admissions to hospital because of diarrhoea; the type of feeding (breast or bottle, or both) being used on admission to hospital; and the duration of breast feeding. The brand of milk being used on admission and the number of bottles and teats and the method of sterilisation employed were also ascertained. It was also determined whether water was administered to the infant other than as milk, the source of drinking water, whether it was boiled or unboiled (filtered, unfiltered, or mineral) and whether water was given during each episode of fever, diarrhoea, or vomiting.

Stool culture and microscopic examination were undertaken at least three times after admission, but virological investigation was not possible. Infants with chronic diarrhoea—that is, lasting more than 10 days, infants weighing less than 2·5 kg or requiring incubator care at birth, and infants showing developmental delay or anomalies were excluded from analysis of the results.

The questionnaries were analysed by computer and included tabulations and χ^2 analysis.

Results

Sex, age group, and type of feeding. Two hundred and four infants were admitted (124 boys and 80 girls), of whom 59 (29%) were breast fed, 115 (56%) artificially fed, and 30 (15%) were on mixed feeding (breast and artificial) at the time of admission. Forty five (22%) were aged 1–3 months, 49 (24%) were aged 3–6 months, 56 (27%) were aged 6–9 months, and 54 (27%) were aged 9–12 months.

Infants from all age groups were admitted in equal ratios. More boys than girls were admitted in each group, but the difference was not significant. There was no association between type of feeding and age groups or sex.

Type of drinking water given between feeds. In all, 199 (98%) mothers gave water between feeds, with only five giving none. Among those who gave water, 30 (15%) gave water after boiling, 97 (49%) gave filtered (unboiled) water, 51 (26%) gave unfiltered (unboiled) water, and 21 (11%) gave unboiled mineral water.

The difference in water use among mothers with different feeding practices was significant. Only five infants did not receive any extra drinking water, and all of these were breast fed and aged between 2 and 6 months. The use of boiled water was four times more prevalent among bottle than breast fed infants (breast fed 5%, bottle fed 20%, and mixed feeding 13·5%). Filtered water was used in similar percentages of infants on the different types of feeding (breast fed 51%, bottled fed 48%, and mixed feeding 40%). The unfiltered water was used in various percentages (breast fed 29%, bottle fed 19%, and mixed feeding 40%). The mineral water was used more often in infants who were bottle fed (13%) than in infants who were breast fed (7%) or on mixed feeding (6·5%).

Socioeconomic class of father. Breast feeding has been shown to be significantly higher among infants of social classes IV and V than of social classes I, II, and III ($p<0·001$).[1]

The difference in water used among different social classes was significant ($p<0·001$), except for the use of filtered water, which was similar in each class (range 41–57%). Of 36 infants from social classes I and II, 10 (28%) received mineral water, nine (25%) received boiled water, only one received unfiltered water, and one received no water at all. Of 82 infants from social class III, 18 (22%) received boiled water, nine (11%) received mineral water, and eight (10%) received unfiltered water. Of 86 infants from social classes IV and V, however, 42 (49%) received unfiltered water, three (3%) received boiled water, two (2%) received mineral water, and four (5%) infants received no water.

Maternal education. The difference in water use among mothers with varying levels of education (grouped as illiterate, primary, secondary, or university) was significant ($p<0·001$). It was broadly similar to the social class distribution. Mothers from each group give filtered water in nearly equal percentages (range 44–48%). Of 108 mothers classed as illiterate, however, 48 (44%) gave unfiltered water, seven (6%) gave boiled water, four (4%) gave no water, and only one gave mineral water. Of 48 mothers with some education (primary or intermediate), 11 (23%) gave boiled water, seven (15%) gave mineral water, and three (6%) gave unfiltered water to their infants. Of 48 mothers with higher education (secondary or university), all gave some water, 13 (27%) gave mineral water, 12 (25%) gave boiled water, and no one gave unfiltered water.

Amount of water given during episodes of fever, vomiting, or diarrhoea. Although most mothers gave water on most days, only 58 (29%) considered it necessary to give water 'always' during episodes of fever, vomiting, or diarrhoea, 85 (42%) gave water 'sometimes', and 61 (30%) did not give any extra water. The difference in water use during episodes of fever, diarrhoea, or vomiting among mothers with different feeding practices was significant ($p<0·001$). Twenty five (42%) of the breast feeding mothers gave no extra water during an attack compared with 26 (23%) of mothers who bottle fed and 10 (33%) of those giving mixed feeds. Some mothers thought water would aggravate vomiting or diarrhoea.

Re-admitted infants. Thirty nine (19%) infants had more than one re-admission to hospital. No association was found between re-admission and age group or sex. Some association between re-admission and type of feeding, however, was apparent, though this was not significant. Nine (15%) breast fed infants, 27 (23%) bottle fed infants, and three (10%) infants on mixed feeding were re-admitted to hospital.

An association between social class and re-admission was noted, though again this did not reach significance. Five (14%) of the 36 infants in social classes I and II, 18 (22%) of the 82 in social

Table *Re-admission rates among infants receiving different types of feeding and water*

	No (re-admission %) of infants classed according to type of water received					*Total No (re-admission %) of infants (n=204)*
	No water	*Boiled*	*Filtered*	*Unfiltered*	*Mineral*	
Breast	5 (0)	3 (0)	30 (13)	17 (18)	4 (50)	59 (15)
Bottle	—	23 (22)	55 (15)	22 (46)	15 (27)	115 (24)
Breast + bottle	—	4 (0)	12 (8)	12 (17)	2 (0)	30 (10)
Total	5 (0)	30 (17)	97 (14)	51 (30)	21 (29)	204 (19)

class III, and 16 (19%) of the 86 infants in social classes IV and V were re-admitted.

There was no association between maternal education and re-admission. Twenty two (20%) infants of mothers classed as illiterate, nine (19%) infants of mothers classed as of primary or intermediate education, and eight (17%) infants of mothers classed as of secondary or university education were re-admitted.

Type of drinking water and re-admission however, were associated (Table). Of five infants aged 2–6 months who were breast fed and receiving no extra water, none were re-admitted. Of 30 infants having boiled water only, five (22%) of 23 infants who were bottle fed were re-admitted. No re-admissions were reported among breast fed infants or infants on mixed feeding. For the 97 infants on filtered water, re-admission was similar for the different types of feeding (breast fed 13%, bottle fed 15%, and mixed feeding 8%) For the 51 infants on unfiltered water, the chance of re-admission was three times higher in bottle fed infants than in breast fed infants or infants on mixed feeding (breast fed 18%, bottle fed 46%, and mixed feeding 17%). Of 21 infants on mineral water, re-admission was twice as common in breast fed as in bottle fed infants.

There was a positive association between the number of bottles used and the frequency of admission ($p<0{\cdot}001$). Out of 88 infants who had between one and three bottles, nine (10%) were re-admitted, and out of 57 infants having more than four bottles, 18 (32%) were re-admitted.

There was no association between re-admission and the type of micro-organisms detected in the stools.

Microbiological analysis of stool. Stool specimens were positive for micro-organisms in only 26 infants. Nine grew pathogenic *Escherichia coli,* nine *Salmonella* species, two *Shigella* species, and six *Giardia lamblia.* There was no association between positive stool culture and water use, type of feeding, or maternal education, though a relative association with social class was apparent. Infectious diarrhoea was higher among the lower social classes ($p=0{\cdot}06$).

Discussion

In this study of 204 infants existing feeding practices in the two hospitals (breast 29%, bottle 56%, and mixed 15%) were no different from those described in a community study of 966 infants in the same age group of less than 1 year (breast 32%, bottle 58%, and mixed 10%).[2] There seemed to be some association between admission and feeding practice, but this was not significant.

The results of this study suggest that many factors other than breast feeding are associated with frequency of infant admission for acute diarrhoea. Breast feeding did not seem to be protective against either single or multiple admissions if water was given as a supplement. The highest rate of re-admission was among infants on bottle feeding who received unfiltered water and infants on breast feeding who received mineral water; the lowest rate of readmission was among infants on breast feeding who received boiled water.

A recent study by Taylor *et al* showed that admissions to hospital for gastroenteritis in the first year of life were marginally less likely in breast fed infants.[3] In a similar survey in New Zealand, which investigated a wide range of gastrointestinal illnesses, there seemed to be some protective effect from breast feeding.[4 5] This effect was restricted, however, to the first four months of life. Other studies in the UK and United States assessing the role of breast feeding in rates of hospital admission for gastroenteritis have shown conflicting results, some showing a benefit (usually without sufficient consideration of possible confounding associations)[6–9] and others showing no protection.[10 11] In the present study more than half of the mothers classed as illiterate were exclusively breast feeding their babies and giving unboiled (unfiltered) water for drinking. Yet the overall frequency of re-admission was not significantly higher from this group than from the other groups. On the other hand, the infants of educated mothers were mostly fed artificially using predominantly boiled or filtered water. The overall frequency of re-admission in these infants was lower, unless mineral water was used, which doubled the frequency of admission. Frequency of admission was significantly associated with the number of bottles used (more than three bottles). It may have been that the more bottles used the less carefully they were sterilised.

Mothers who breast fed infants used significantly less drinking water on ordinary days and during episodes of fever, diarrhoea, or vomiting, probably because of low demand or unavailability of feeding bottles: mothers giving artificial feeding alone or as a supplement used water more often. This could be another reason that fewer breast fed infants were admitted, as fewer were exposed to contaminated water and utensils. In a recent case control study of cholera in infants from Bahrain Gunn *et al*[12] did not determine whether breast milk had a physiological preventive effect or whether its use simply minimised exposure to contaminated liquids and food.

Although in almost all studies different types of feeding were treated as separate variables, this does not necessarily mean that the infant received nothing else. As is shown in the present study, 98% of mothers gave water to their infants because of the hot climate, even though they were breast fed. Both the factors of exposure to the contaminated bottles and the use of unsuitable unboiled (unfiltered or mineral) water for infants were unavoidable.

There is no evidence that mineral water does not contain micro-organisms, as not every bottle can be analysed microbiologically. The chance of survival of micro-organisms in mineral water depends largely on its pH and whether it is aerated. In general, survival of enteric bacteria decreases at pH values below 5·0, but the pH of most mineral water ranges from 7·2–7·8.

Most of the published studies have related diarrhoea simply to breast or bottle feeding without considering mixed feeding. This study showed that fewer infants on mixed feeding were re-admitted, though the differences did not reach significance. Cullinan found that the incidences of symptoms of 'running nose', 'colic', and 'thrush' were lowest among babies on mixed feeding.[13]

It has been said that breast milk is the best infant food where water supplies are bad and hygiene is difficult. This study, however, showed that breast feeding is not sufficient protection, as no infant is exclusively breast fed after the neonatal period. Water hygiene is probably the key factor in decreasing the incidence of diarrhoeal disease.

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Favourable prognostic features in histiocytosis X: bone involvement and absence of skin disease

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SUMMARY The records of 70 patients presenting to this hospital since 1961 with histiocytosis X confirmed by biopsy examination have been reviewed. The patients were subdivided into three groups: group A, those under 2 years of age at diagnosis; group B, those between 2 and 5 years; and group C, those over 5 years. All eight patients who died (11% overall mortality) were under 2 years of age at diagnosis. Involvement of lung, liver, and bone marrow were confirmed as poor prognostic features. The presence of bone disease and absence of skin rash were identified as favourable features.

Langerhans' cells, Kupffer's cells, bone osteoclasts, microglial cells, and alveolar macrophages together with circulating monocytes are all histiocytes and are derived from a bone marrow stem cell.[1] Histiocytes are also found in pleura, peritoneum, lymph nodes, and spleen. The disease histiocytosis X can affect any of these organs and therefore has a wide clinical range. Although aetiology and treatment remain controversial,[2] there is uniform agreement with Komp[3] and Lahey[4] that young children under 2 years of age with vital organ (lung, liver, and bone marrow) dysfunction fare badly, with a 10–20% mortality. At the other end of the range, patients with single system bony disease have negligible mortality, although morbidity may be considerable.[5 6] These facts have led me to question whether the presence of bone disease in an otherwise poor prognostic group confers a more favourable outcome. Skin disease is the next most common presenting feature after bone disease but its importance as a prognostic factor has not been previously assessed.

Patients and methods

The records of 70 patients with histiocytosis X confirmed histologically attending this hospital between 1961 and 1982 were reviewed to determine the incidence of specific disease manifestations at diagnosis and to establish their relative prognostic importance. For comparison with the prognostic groups described by Komp[3] and Lahey,[4] the patients were subdivided into three groups: group A, those patients under 2 years at presentation; group B, those from 2 to 5 years, and group C, those over 5 years.

Tests for significant prognostic differences between groups of patients with different presenting features were carried out using either the χ^2 test, incorporating Yates's correction for continuity, or with small samples the Fisher exact probability test on 2×2 contingency tables.

Results

The age range extended from <1 month, four children having been born with skin disease, to 14 years. Forty two patients were boys, which was in line with a reported 2:1 male:female preponderance.[6] Twenty patients had single system and 50 multisystem disease. The number of patients in each of the groups is given in Table 1.

Mortality. Eight patients (five boys and three girls) in the study died, an overall mortality of 11%. All of these patients were in group A and all had multisystem disease with involvement of vital organs (lung,

Table 1 *Details of the study groups*

Group	*Age (years)*	*Total*	*Boys*	*Girls*	*Deaths*
A	<2	40	22	18	8
B	2–5	15	7	8	0
C	>5	15	14	1	0
Deaths		8	5	3	

liver, and bone marrow). One child died at the age of 4 years but originally presented at 1 year with skin and scalp rash, widespread bony lesions, bone marrow infiltration, diabetes insipidus, and failure of growth hormone. At postmortem examination she was found to have widespread disease, including involvement of dura, pericardium, and gut. All the other children died before reaching 2 years of age.

Bony disease. Bone involvement was identified in 82% of patients studied. Flat bones, especially the skull, were involved more often than long bones. A soft tissue swelling invariably overlaid a typical radiotranslucent area on *x* ray film and produced symptoms depending on its location. These included proptosis from periorbital disease, suppurative mastoiditis from temporal bone involvement, and loss of teeth from gum disease. The axial skeleton was the next commonest site of bony lesions followed by the long bones. Lesions at these sites gave rise to regional pain and stiffness and resulted in voluntary immobilisation of the affected area.

Only five (16%) of the 32 patients with bony disease in group A had single system disease, whereas 10 (76%) out of 13 with bony disease in group C had single system disease. Of the 12 patients with multisystem disease who did not have bone involvement, four (33%) died, whereas of 38 patients who had multisystem disease that included bony disease only four (11%) died. This difference was significant (p<0·02) using the χ^2 test on a 2×2 contingency table. For group A the difference was even more pronounced (50% (four of eight) of the patients with multisystem disease without bone involvement died, whereas only 15% (four of 27) of those with bone involvement died; Table 2). The smaller sample size, however, meant that this difference was not significant (p=0·522).

Skin disease. Thirty eight patients presented with skin involvement, an overall incidence of 54%. Four babies were born with skin lesions. Skin disease was always an initial presenting feature. In no case did it first occur during subsequent course of the disease. There was a higher incidence of skin rash in group A (68%) than in groups B and C (Table 3). The rash varied from a few discrete pinhead lesions confined to the trunk to severe flexural eczematous lesions to florid haemorrhagic confluent weeping areas with crusting. The scalp rash was usually mistaken for chronic seborrhoeic dermatitis or 'cradle cap'.

Generalised skin disease at presentation was a poor prognostic factor. All patients who died had this feature, and the overall mortality for those with skin disease was 21%. None of the patients presenting without skin disease died. The significance of this difference using the χ^2 test was p<0·025. Although skin disease was more common in the youngest, highest risk age group (group A), those presenting without skin disease within this group were significantly more likely to survive (p=0·029, using the Fisher exact probability test; Table 3).

Involvement of vital organs. For the purpose of this study involvement of vital organs comprised bone marrow, liver, and lung as in most large series dysfunction of these organs is a poor prognostic feature. Involvement of vital organs was found most exclusively in group A, with lungs being the commonest organ involved at presentation. Only four children in group B presented with involvement of vital organs. Two children in group C presented with this feature and again the organ involved was the lung. Chest *x* ray films were used to assess involvement, with lung function testing being used in only a few patients. Liver function tests were usually only performed if there was clinical enlargement of the organ, and a bone marrow aspiration was performed if the peripheral blood count was abnormal in any way.

All the patients who died developed dysfunction of vital organs during the course of their disease, but

Table 2 *Incidence of disease involving bone in the three study groups. Numbers in parentheses are deaths*

	Total patients	*Multisystem disease*		*Single system disease*
		No bony disease	*Bony disease*	
Group A	40 (8)	8 (4)	27 (4)	5 (0)
Group B	15 (0)	2 (0)	8 (0)	5 (0)
Group C	15 (0)	2 (0)	3 (0)	10 (0)
Total	70 (8)	12 (4)	38 (4)	30 (0)
% Deaths	11	33	11	0

Difference between deaths with no bony disease compared with deaths with bony disease, p<0·02.

Table 3 *Incidence of skin disease in the three study groups. Numbers in parentheses are deaths*

	Total patients	*No with skin disease*	*No without skin disease*	*% With skin disease*
Group A	40 (8)	27 (8)	13 (0)	68
Group B	15 (0)	8 (0)	7 (0)	53
Group C	15 (0)	3 (0)	12 (0)	20
Total	70 (8)	38 (8)	32 (0)	54
% Deaths	11	21	0	100

Difference between deaths with skin disease compared with deaths with no skin disease, p<0·025.

Table 4 *Involvement of vital organs in the three study groups*

	Total patients	*Organ involved*		
		Lungs	*Liver*	*Bone marrow*
Group A	40	11	10	9
Group B	15	2	1	1
Group C	15	2	0	0
Deaths	8	8	8	8

bone marrow and liver dysfunction were rare presenting features (Table 4).

Discussion

Identification of prognostic groups within the disease range of histiocytosis X has become more important with the changing concept of the disease from malignancy to an intercellular communication disorder.[2] It is no longer justifiable to treat this non-malignant disease with potential carcinogens, so that cytotoxic drugs are becoming reserved for very poor prognostic cases who do not respond to steroids. Prognostic groups have previously been described by Komp[3] and Lahey.[4] This study confirms that children under 2 years of age with involvement of vital organs form the poorest prognostic group. Within this group have been identified two other features of prognostic importance — presence of bony disease and skin rash at diagnosis.

Patients with disease totally confined to bone do well and require no treatment provided that the bone involved is not weight bearing or surrounding a vital structure, such as the optic nerve or spinal cord. Those patients in this series who had bone involvement as part of multisystem disease had a more favourable outcome than those who did not, and this was most pronounced in the youngest age group.

In this series skin involvement at diagnosis was most common in the youngest age group and carried a considerably worse prognosis within this group. It was invariably part of multisystem disease.

In a disease characterised by spontaneous remissions and relapses assessment of therapeutic regimens is difficult. Both combination and single agent chemotherapy are associated with short and long term side effects,[7] which may not now be acceptable with the changing concept of the disease. Undoubtedly, children have been overtreated in the past. Very young children with multisystem disease, which includes bony disease, may not require potentially toxic treatment, but those without bone involvement who have vital organ disease, including skin disease, are the group with highest mortality and may benefit from new approaches to treatment.

I acknowledge the encouragement and support of Dr J Pritchard in the preparation of this paper.

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Short reports

Diabetes insipidus and occult intracranial tumours

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SUMMARY We describe four patients with intracranial tumours who presented with diabetes insipidus and subsequently developed an evolving anterior pituitary endocrinopathy. The delay in imaging the tumours varied between 2·1 and 11·2 years (mean 5·4 years).

Most pituitary endocrine deficiencies of childhood are idiopathic,[1] but central nervous system lesions[2] as well as idiopathic disease may produce a progressive loss of pituitary function with time (evolving endocrinopathy). The association of diabetes insipidus with evolving anterior pituitary endocrinopathy is sinister and points to the presence of an hypothalamopituitary tumour;[1] such tumours usually manifest their presence within four years of the onset of diabetes insipidus.[3]

We present four cases of diabetes insipidus secondary to occult intracranial tumours and discuss features that may help diagnosis.

Case reports

Case 1. This girl was referred when aged 11·8 years because of secondary enuresis and polydipsia from the age of 3 years and the onset of growth failure between 6 and 7 years. At 12·2 years (Table) an inadequate growth hormone response to insulin induced hypoglycaemia (peak growth hormone <1 mU/l) was produced in addition to an abnormal plasma thyroid stimulating hormone (TSH) response to intravenous thyrotrophin releasing hormone (TRH) (basal TSH 5·0 mU/l, rising to 16 mU/l at 20 minutes and 22 mU/l at 60 minutes after TRH 200 μg). Secretion of gonadotrophin, prolactin, and cortisol was normal. Fundoscopy, visual fields, skull *x* ray, and computed tomography of the hypothalamopituitary region showed no abnormality. She was treated with human growth hormone and 1-deamino-8-D-arginine vasopressin (DDAVP). On this regimen her growth accelerated from 2·3 to 8·7 cm/year. At 14·2 years she remained prepubertal. Morning plasma cortisol concentration was low (140 nmol/l at 0800h), indicating adrenocorticotrophic hormone (ACTH) deficiency, and serum thyroxine concentrations (55 nmol/l) had fallen below normal. Fundoscopy, visual fields, and skull *x* ray remained unchanged, but a further computed tomogram revealed a small hypothalamic tumour, which was treated by radiotherapy without biopsy examination. Puberty was induced by administration of oestrogen and a computed tomogram, at 17 years, showed no evidence of a tumour.

Case 2. This boy presented at 6·6 years of age with an 18 month history of polyuria and polydipsia. Height was on the 50th centile with a normal growth velocity. Plasma cortisol (900 nmol/l) and serum

Table *Clinical and endocrine data for four patients with diabetes insipidus due to intracranial tumours*

Case No	*Sex*	*Age at onset of diabetes insipidus (years)*	*Age at onset of growth failure (years)*	*Age at detection of anterior pituitary endocrinopathy (years)*				*Age at diagnosis of intracranial tumour (years)*	*Delay from symptoms to diagnosis (years)*
				Growth hormone	*TSH*	*ACTH*	*Gonadotrophins*		
1	F	3·0	6 to 7	12·2	12·2	14·2	14·2	14·2	11·2
2	M	5·1	Normal growth	Normal	6·6	8·0	?	8·0	2·9
3	F	6·7	6·7	7·7	12·2	12·2	12·2	12·2	5·5
4	F	6·0	7·0	7·3	8·1	8·1	?	8·1	2·1

ACTH=Adrenocorticotrophic hormone; TSH=Thyroid stimulating hormone.

growth hormone (>40 mU/l) responses to insulin induced hypoglycaemia were normal. Plasma TSH showed an abnormal response, however, to intravenous TRH (basal TSH <1 mU/l, rising to 3·7 mU/l at 20 minutes and 5·7 mU/l at 60 minutes), although serum thyroxine concentration (73 nmol/l) was normal. Computed tomography of the hypothalamopituitary region showed no abnormality. Treatment was begun with DDAVP. At 8 years a low morning plasma cortisol concentration (150 nmol/l at 0800h) indicated probable ACTH deficiency, but secretion of growth hormone was normal. Skull *x* ray showed enlargement of the pituitary fossa, and a small suprasellar mass was shown on computed tomography. Transsphenoidal exploration revealed a craniopharyngioma, which was partially resected, and radiotherapy was administered postoperatively.

Case 3. This girl presented at 6·7 years with diabetes insipidus and growth failure. Growth hormone deficiency (peak <1 mU/l) was shown in response to hypoglycaemia; other tests of anterior pituitary function, including serum prolactin, were normal, as were computed tomograms at 7, 7·5, and 8 years of age. At 9 years an air encephalogram and further computed tomogram (Figure) were normal. When aged 10 years she began treatment with human growth hormone, and although she remained prepubertal, her growth rate accelerated from 2·9 to 6·4 cm/year. At the age of 12 she was investigated because of headaches and growth arrest while on treatment with human growth hormone. Endocrine assessment revealed ACTH deficiency (plasma cortisol 130 nmol/l at 0800h), abnormal response to intravenous TRH (basal TSH 1·8 mU/l, rising to 24 mU/l at 20 minutes and 69 mU/l at 60 minutes), and hyperprolactinaemia (serum prolactin 1540 mU/l). Examination of her visual fields showed bitemporal hemianopia with a red target. Skull *x* ray was unchanged but a further computed tomogram (Figure) showed a tumour of the third ventricle. She was treated with radiotherapy without biopsy examination.

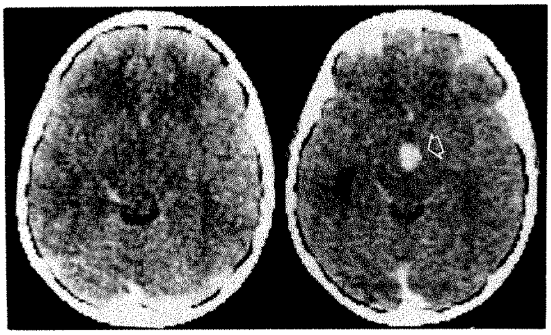

Figure *Enhanced computed tomogram (EMI) images in horizontal section from case 3 at the level of the third ventricle. The image on the left was taken at age 9 years, that on the right at 12 years when an enhancing lesion in the region of the third ventricle (arrow) was imaged.*

Case 4. A girl of 7·2 years was referred with a 1·2 year history of polydipsia, polyuria, and growth failure. Impaired secretion of growth hormone (peak 12 mU/l) was obtained in response to hypoglycaemia, but no other anterior pituitary dysfunction was shown. Fundoscopy, visual fields, and skull *x* ray film yielded normal results. She was treated with DDAVP. At 8·1 years her growth had decelerated to less than 2 cm/year. Repeat pituitary function tests showed that her endocrine state had altered. Her peak growth hormone response to hypoglycaemia was only 3·6 mU/l and in addition there was an inadequate plasma cortisol response (peak 210 nmol/l). Serum thyroxine concentration (48 nmol/l) was subnormal. A lateral skull *x* ray film showed no abnormality, but an air encephalogram showed a suprasellar mass, which was inoperable at surgery, and no biopsy examination was performed. Cranial irradiation was given postoperatively. At age 12·6 years a tumour recurrence was treated by insertion of a ventricular-atrial shunt and further cranial irradiation. Unfortunately, she developed spinal metastases and died at 13 years.

Discussion

All four patients had diabetes insipidus and subsequently showed an anterior pituitary endocrinopathy that evolved with time. The endocrinopathy may have been underestimated by the difficulty in diagnosing gonadotrophin deficiency in prepuberty. We emphasise the necessity to reassess anterior pituitary function with time. Growth response to treatment with human growth hormone may be unimpaired (cases 1 and 3) in the presence of an untreated intracranial tumour, although this response may be temporary (case 3). In one patient impairment of growth while on treatment with human growth hormone and the development of a visual field defect provided clues to the diagnosis, while in the other three children the diagnosis was made on follow up neuroradiology. One patient (case 2) was unusual in having neither growth failure nor growth hormone deficiency.

Initial neuroradiology, which included computed tomography in three patients, yielded normal results. The subsequent imaging of an intracranial tumour was made on the basis of change in the lateral skull *x* ray film in one patient or by changes in the computed tomogram or air encephalogram in the other three patients. Case 3 required five sequential computed tomograms and an air encephalogram during a period of 5·5 years before the tumour was imaged. In two of our patients (cases 1 and 3) the interval between the onset of symptoms and diagnosis was greater than four years,[3] and in one this delay was 11·2 years. This delay occurred in spite of the recent technological advances in neuroradiological imaging.

These cases illustrate the importance of both endocrine and neuroradiological follow up in children with apparently isolated diabetes insipidus, particularly if the risk of permanent visual loss due to a tumour is to be avoided. While diabetes insipidus may be familial[4] or associated with other congenital abnormalities of the brain,[5] the more usual aetiologies are those of intracranial tumour or histiocytosis. The onset of diabetes insipidus in mid-childhood—especially if combined with growth failure—should never be considered idiopathic. Such cases require careful follow up using high resolution computed tomography[6] and possibly nuclear magnetic resonance imaging, if necessary into adult life.

We are grateful to Dr D M Flynn, The Royal Free Hospital, London, for his help with case 3.

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Height in epilepsy

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SUMMARY Longitudinal data on the height of prepubertal children with epilepsy are presented. Although both seizures and antiepileptic drugs may affect serum hormone concentrations, linear growth remains normal.

Serum hormone concentrations can be affected by both seizures[1] and antiepileptic drugs.[2] Suboptimal adult height after somewhat early puberty has been reported in children who attended a residential school because of epilepsy.[3] We report on the stature of children with chronic seizure disorders who live at home and attend local schools.

Patients and methods

The medical records of all children with epilepsy who attended the paediatric neurology clinic at our hospital between May and July 1985 were examined. The present data relate to 51 children (29 girls) who had been assessed when aged 2 to 11 years. Clinical details are given in the Table. Measurements for standing height, using a Harpenden Stadiometer, were available at six monthly intervals. Data from boys and girls were analysed separately.

As calculation of mean trends in mixed longitudinal data, based on mean values at each age, gives inefficient estimates[4] the age at which the largest numbers of children were measured was selected (8·0 years for girls and 9·5 years for boys) and the mean heights at this age calculated. Individual increments in height were calculated for each six months and the mean increment successively added to or subtracted from the mean height referred to previously.[5] This method obviates bias effects from single height measurements from unusually tall or short children. More boys and girls were older rather than younger than the reference age. Data were available at 11 years for 14 boys and 10 girls. The parental heights were ascertained in eight cases in whom seizures had been life long and measurements were available at 11 years.

Table *Clinical details of the subjects studied*

	Boys (n=22)	*Girls (n=29)*
Predominant seizure type:		
Generalised tonic-clonic	5	5
Myoclonic syndrome	7	7
Absence	1	3
Simple partial	—	2
Complex partial	8	12
Photosensitive	1	—
Antiepileptic drug treatment:		
None	1	—
Barbiturates (including primidone)	7	2
Phenytoin	6	9
Carbamazepine	8	15
Valproate	8	12
Ethosuximide	1	2
Benzodiazepines	8	6
Receiving two drugs	10	14
Receiving three or more drugs	2	2
Age at onset of seizures:		
Before 2 years	13	16
Before 5 years	18	18
Before 7 years	20	23

Results

Figures (a) and (b) show the mean standing heights plotted at six monthly intervals for boys and girls, respectively. The longitudinal curve for boys was between the 25th and 50th centiles for normal boys aged 2 to 11 years. For girls, the growth curve was between the 50th and 75th centiles. There is no evidence of an early onset of pubertal growth in either sex. The eight children measured at 11 years whose seizures had started in infancy and for whom parental heights were available were growing in keeping with their familial expectations. Subgroups of children with a specific type of seizure, with a high seizure frequency, or receiving particular antiepileptic drugs had growth curves similar to the total group.

Discussion

Early puberty and suboptimal height attainment has been noted in children with epilepsy in a residential school.[3] It has been suggested that the epilepsy in these cases might be particularly severe as only 0·5% of British children with epilepsy attend residential schools. Many of the children in the present study were severely affected and were having frequent daily seizures, but they were living at home and attending day schools. Their growth pattern throughout childhood was within normal limits and puberty did not occur early. It is concluded that seizure frequency does not influence height attainment and that the suboptimal growth of children educated away from home may be related more to concurrent social problems than to epilepsy.

A rise in serum prolactin concentration follows generalised tonic-clonic seizures.[1] Although the rise in growth hormone concentrations is less consistent, there is increased growth hormone responsiveness to stimulation with clonidine after seizures.[1] Despite

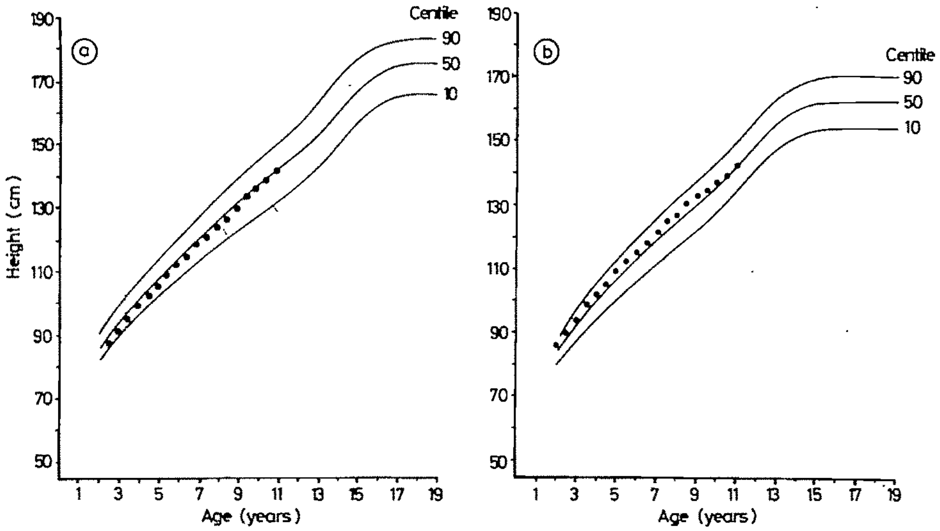

Figure *Linear growth in (a) boys and (b) girls with epilepsy. The normal 10th, 50th, and 90th centiles from Tanner height standard charts are shown for comparison.*

these reports, we found no evidence that the growth in children with frequent generalised tonic-clonic seizures was impaired relative to those who had infrequent partial seizures.

Phenytoin, phenobarbitone, carbamazepine, and valproate increase the metabolism of sex hormones and enhance the synthesis of sex hormone binding globulin in the liver.[2] In boys the increase in sex hormone binding globulin leads to an increase in total testosterone concentration, but the concentration of the free fraction remains unaltered.[2] In adult women increases in serum growth hormone have been noted during treatment with carbamazepine and phenytoin, but the rise in growth hormone caused by insulin hypoglycaemia may be less than expected in adults on antiepileptic drugs.[2] Comparable data are not available for children. It has been postulated that short stature, which has been reported in adult men with epilepsy,[6] might be consequent on the use of phenytoin in childhood, but our evidence suggests that antiepileptic drugs do not have clinically important effects on height attainment up to puberty.

The helpful advice from Professor MA Preece for the analysis of the growth data is gratefully acknowledged.

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Preoperative stabilisation in congenital diaphragmatic hernia

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SUMMARY Critically ill infants with congenital diaphragmatic hernia were treated by either early surgery or delayed surgery after preoperative stabilisation. The preoperative stabilisation was aimed at correcting acidosis and hypoxia, thereby reducing the severity of persistent fetal circulation. Survival improved from 12·5% after early surgery to 52·9% after delayed surgery.

Infants with congenital diaphragmatic hernia often have severe acidosis and hypoxia at presentation. Immediate repair may lead to an improvement, but many infants deteriorate with increasing hypoxia, dying after a 'honeymoon period' of about 18 hours. This deterioration is usually due to persistent fetal circulation, which is a consequence of hypoxia, acidosis, and the innately abnormal pulmonary arterioles, which are more muscular and reduced in number.[1 2] Recent reports have suggested that preoperative treatment aimed at correcting acidosis, hypoxia, and tissue hypoperfusion decreases the severity of persistent fetal circulation and improves survival.[3–5] In 1983 we adopted this new management approach. This paper reports our results.

Patients and methods

From January 1981 to November 1985, 33 infants with congenital diaphragmatic hernia presenting within two hours of birth were treated in our department; their details are shown in Table 1.

Before August 1983, 16 infants were treated with early surgery. Preoperatively most were ventilated only briefly while surgery was organised. Stomach aspiration was used to decompress the bowel. Metabolic acidosis was treated with sodium bicarbonate.

After August 1983, 17 infants were treated with delayed surgery after a period of preoperative stabilisation. Infants in respiratory failure were paralysed with tubocurare and ventilated using low pressures and high rates. Stomach aspiration was again performed. Arterial and venous catheters were inserted through the umbilical vessels. The

Table 1 *Details of infants with congenital diaphragmatic hernia presenting within two hours of delivery*

	Surgery	
	Early *(n=16)*	*Delayed* *(n=17)*
Gestation (weeks):		
Mean (SD)	38·9 (2·4)	37·5 (2·6)
Range	31–42	32–40
Birth weight (g):		
Mean (SD)*	3170 (630)	2690 (680)
Range	1700–4140	1750–3670
Female:male	8:8	6:11
Inborn:outborn	6:10	9:8
Left:right hernia	15:1	13:4
Mean (SD) Apgar score at one minute	4 (1·7)	3·9 (1·9)
Congenital heart disease	2	3
Prematurity	1	5

*$p<0{\cdot}05$.

partial pressure of oxygen in post-ductal blood was monitored using the arterial catheter (Searle) and in pre-ductal blood using a transcutaneous oxygen electrode. If hypoxia could not be corrected by ventilation tolazoline (1–2 mg/kg/h) was given. Circulatory failure was treated with plasma and dopamine (2–10 mcg/kg/min) and metabolic acidosis with sodium bicarbonate. The stabilisation procedure lasted four to 16 hours and the infant proceeded to surgery when his condition was considered optimum.

At operation the diaphragm was usually sutured directly, but if the defect was too large a prosthetic graft was used. If the abdominal wound could not be closed a similar graft was inserted. An ipsilateral chest drain with an underwater seal was used without suction.

Postoperatively, all infants received ventilation, dopamine, tolazoline, and sodium bicarbonate, as necessary. Central venous pressure monitoring in the group who received delayed surgery allowed for more accurate fluid management. In particular, plasma was used more liberally to replace losses from the wound. Paralysis was stopped when an improvement in ventilation was seen, which was usually after several days.

Statistical analysis was by Student's unpaired *t* test and χ^2 analysis with Yates's correction.

Results

Details of treatment and outcome are summarised in Table 2. The preoperative pH was significantly better in the group who received delayed surgery ($p<0{\cdot}001$), and all infants with a preoperative pH<7·2 died. The prevalence of contralateral pneumothorax decreased from six after early surgery to one after delayed surgery; all seven infants died. Survival improved from 12·5% after early surgery to 52·9% after delayed surgery ($p<0{\cdot}05$). Five infants had congenital heart disease and they all died. When these five infants were excluded survival rates were 14·3% after early surgery and 64·3% after delayed surgery ($p<0{\cdot}05$). Ventilation from birth was required in 22 infants; all 10 in the group who received early surgery died, whereas four of the 12 in the group who received delayed surgery survived, two of them despite being profoundly acidotic with a pH of 6·85 and 6·98 shortly after birth.

Discussion

This study suggests that a period of treatment aimed at correcting acidosis, hypoxia, and hypoperfusion preoperatively is associated with improved survival of critically ill infants with congenital diaphragmatic hernia. Ventilation was most effective and the prevalence of pneumothoraces lower if the infant was paralysed and a rate of roughly 60 breaths per minute used. The infants usually improved considerably after several hours of efficient ventilation, and some required no other preoperative treatment. Other infants had metabolic acidosis due to low cardiac output and tissue hypoperfusion. This could usually be corrected preoperatively by giving plasma and sodium bicarbonate, but it often recurred

Table 2 *Treatment and outcome in infants presenting with congenital diaphragmatic hernia within two hours of delivery*

	Surgery	
	Early *(n=16)*	*Delayed* *(n=17)*
Preoperative treatment:		
Ventilation	14	17
Dopamine	1	2
Tolazoline	0	4
Paralysis	0	11
Plasma	2	7
Sodium bicarbonate	10	11
Highest preoperative pH†:		
Mean (SD)*	7·04 (0·21)	7·30 (0·11)
Range	6·77–7·45	7·14–7·47
Postoperative treatment:		
Ventilation	13 (1 died during operation)	16 (1 died before operation)
Dopamine	10	10
Tolazoline	10	12
Paralysis	2	16
Survivors:**	2	9

*$p<0{\cdot}001$ By Student's *t* test.
**$p<0{\cdot}05$ By χ^2 test with Yates's correction.
†Arterial pH.

during the operation. Infants with left sided diaphragmatic hernia often have a mild degree of left ventricular hypoplasia.[6] Their cardiac output is likely to be reduced, so it is not surprising that surgery is poorly tolerated. These infants could probably be helped by the use of dopamine started preoperatively, as used by Nair *et al.*[3]

There was a coincidental increase in the use of abdominal wall grafts in infants treated by delayed surgery. It was our impression that their use benefited a few infants by facilitating ventilation. From autopsy evidence, however, we consider that only one infant not so treated would have benefited from a graft. It is therefore very unlikely that the improved survival was the result of the increased use of grafts.

We recommend that critically ill infants with congenital diaphragmatic hernia who present shortly after birth are stabilised before operation. If with this treatment the acidosis persists, with a pH<7·20, it is very unlikely that surgery will help.

We thank Miss M J Mayell for allowing us to study patients under her care, Dr S J Bodden, who was instrumental in devising the new protocol, and Mrs F Prew for typing the manuscript.

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Neonatal typhoid fever

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SUMMARY Three infants of Pakistani immigrant mothers developed typhoid fever in the neonatal period. All three survived, but two became chronic excretors of *Salmonella typhi*. The risk of an outbreak of typhoid fever in a maternity unit or special care baby unit is emphasised.

Typhoid fever is rare in neonates.[1 2] The public health problems it poses, however, are great. This report describes three neonates with typhoid fever born in two maternity hospitals in Birmingham over the past nine years.

Case reports

Case 1. After a normal birth and 24 hour discharge from Marston Green Hospital, Birmingham, a full term Pakistani girl presented at this hospital, very ill, shocked, and hypothermic at the age of 3 days. She had a 12 hour history of increasing lethargy and poor feeding.

After admission, she had a cardiorespiratory arrest and subsequently needed assisted ventilation for 48 hours because of attacks of apnoea. She also had episodes of clonic seizures and hypoglycaemia. A chest radiograph showed bilateral patchy consolidation. The blood culture grew *Salmonella typhi* phage type E_1 after incubation for three days. Results of lumbar puncture were normal. Repeated stool and urine cultures yielded negative results. Treatment with antibiotics was changed from ampicillin and gentamicin to trimethoprim when the results of the culture were known. Trimethoprim was given for two weeks, during which time she had neither fever nor diarrhoea. At 6 months the infant has microcephaly and neurodevelopmental delay. Multiple stool cultures from the mother and her family have remained negative for *S. typhi*. No cross infection occurred while the baby was nursed in the intensive care unit where a strict hand washing policy was operated, although the baby was not isolated.

Case 2. After three days of intermittent fever a

Pakistani mother who had been in Pakistan three months earlier delivered a boy at 36 weeks' gestation at Marston Green Hospital. She had a postpartum fever (40·8°C) and rigor and was treated with intravenous ampicillin. *S. typhi* of phage type D_5 was isolated from her blood, stools, and urine. Her stool cultures remained positive for four months.

The infant was feverish immediately after birth and developed clinical and radiological signs of respiratory distress syndrome. He needed continuous positive pressure ventilation for 48 hours. On the fifth day the mother and baby were transferred to the infectious diseases unit at this hospital. Ampicillin was given parenterally for one week and orally for another two weeks. Apart from jaundice, intermittent fever, and frequent watery green stools between the fifth and eighth day, the natural history was uneventful. *S. typhi* phage type D_5 was isolated only from the infant's stools. No babies or staff of the special care baby unit were infected. The same organism was isolated, however, in stool specimens from the father and an aunt. At 7 months the infant was still excreting the bacteria. Furthermore, two mothers who had babies at around the same time in the maternity hospital were believed to have acquired *S. typhi* from the index case. A total of six children from these two families had *S. typhi* phage type D_5 isolated from their stools. Two of these children were admitted to hospital with clinical infection.

Case 3. At 48 hours of age a Pakistani boy of 36 weeks' gestation who was born in Dudley Road Hospital, Birmingham, developed a temperature of 37·5°C and had several blood stained mucousy stools. The father had been in Pakistan a month earlier. A stool culture grew *S. typhi* phage type E_1. Blood and urine cultures yielded negative results. The mother was later found to be an asymptomatic excretor of *S. typhi* of the same phage type. The infant was isolated. Intravenous ampicillin was given for seven days followed by oral trimethoprim for another week. The infant was well apart from transient fever (37·5°C) and some loose stools. At 4 weeks of age, however, he was still excreting *S. typhi*. His brother was also found to be an asymptomatic excretor. Stool cultures were not obtained from staff or patients. No cross infection was known to have occurred.

Discussion

Neonatal typhoid fever is usually acquired at birth. Vertical transmission of the infection is suggested in two of our infants by the concordant *S. typhi* phage type in mother and baby. The third infant (case 1) is also likely to have acquired the infection from the mother, despite the lack of a positive maternal stool culture.[3]

The clinical diagnosis may be more difficult to make than in adults. The classical 'rose spots' are not evident, especially in dark skinned infants.[4] The incubation period is shorter and is usually only about 48 hours, although it may be up to seven days.[2] Of eight neonates with enteric fever described by Duggan and Beyer, all had diarrhoea, but only one was febrile, while the others were afebrile or hypothermic.[1] The clinical features in our infants are in keeping with these descriptions.

There is no ideal drug for the treatment of neonatal typhoid fever. Experience is limited to chloramphenicol and ampicillin.[2] The risk of aplastic anaemia and the emergence of chloramphenicol-resistant *S. typhi* have led, however, to the search for alternative antibiotics. In children and adults co-trimoxazole or trimethoprim[5] when given parenterally are of proven efficacy. Our infant with septicaemia responded to trimethoprim given intravenously. Infants with mild *S. typhi* enteritis do not require treatment. The duration of diarrhoea or carrier state is not shortened by treatment with oral antibiotics.[6] Two of our infants remained asymptomatic excretors despite treatment with oral antibiotics.

Our report highlights the health hazards that undetected asymptomatic *S. typhi* excretor mothers can bring to any maternity and baby unit. Only in case 2 was the possible spread of infection pursued vigorously. All the nursing and medical staff and patients in the labour, postnatal, and special care baby unit had stool cultures performed. The organism was isolated in two other mothers, who were discharged, and their families. It was fortuitous that a larger outbreak did not occur. As screening for excretion of *S. typhi* in pregnant mothers is not feasible we suggest that great care is taken when looking after infants with fever and diarrhoea, especially if their mothers are from developing countries.

We thank Dr E E Hill and Dr J G Bissenden for allowing us to include their patients in this report and Dr C J Ellis for advice on management.

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Fluoride treatment in corticosteroid induced osteoporosis

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SUMMARY Severe osteoporosis with multiple vertebral fractures occurred in two girls receiving prolonged high dose corticosteroids for relapsing dermatomyositis. Sodium fluoride, supplemented with calcium and vitamin D, helped control secondary osteoporosis in one case and should be considered as part of the curative treatment of corticoid induced osteoporosis.

Sodium fluoride is now used in idiopathic osteoporosis of aging adults,[1 2] as it should be able to increase bone mass. Prolonged high doses of treatment with corticosteroids may produce severe osteoporosis in children. The histomorphometric and histodynamic method[3] represents a quantitative approach to the evaluation of bone disease under treatment with fluoride.

Case reports

Case 1. A 10 year old, prepubertal girl was treated for dermatomyositis. From August 1980 to December 1982 she received the following treatment and dosages: prednisone 0·6–2 mg/kg/day, with calcifediol 100 µg/day up to November 1981 and then alfacalcidol 0·5–1 µg/day up to December 1982, and also hydrochlorothiazide 75 mg/day. No height gain was observed from January 1981 to December 1982. At this time her height was 128 cm and dermatomyositis was stable, but treatment with corticosteroids induced a severe osteoporosis and multiple vertebral fractures (D6, D7, D10, D12, and L5).

From December 1982 to April 1984 she received prednisone 0·6–1·1 mg/kg/day on alternate days with alfacalcidol (0·5 µg/day), calcium carbonate (1·5 g/day), and hydrochlorothiazide. Sodium fluoride was given at a dose of 1 mg/kg/day for 16 months. The height gain during this treatment was 10 cm and the girl remained impubertal. No other vertebral fractures occurred, and bone *x* ray profile has improved.

Case 2. This 7 year old girl presented with dermatomyosistis in March 1981. She received an average dose of prednisone 1·4 mg/kg/day with alfacalcidol 0·25–0·75 µg/day and hydrochlorothiazide 75 mg/day without calcium supplementation because of hypercalciuria. In October 1982 her height was 123 cm and the presence of multiple vertebral fractures (eight vertebras) revealed a severe osteoporosis associated with renal lithiasis. From June 1983 to May 1985 the dermatomyositis relapsed and treatment included prednisone 1·1 mg/kg/day in conjunction with sodium fluoride 1 mg/kg/day, alfacalcidol 0·5 µg/day, and hydrochlorothiazide 75 mg/day. During this time, the *x* ray profile of the spine improved and no other vertebral fractures occurred. At the end of the study the girl remained prepubertal and her height was 135 cm.

In both cases, after tetracycline double labelling, a bone biopsy specimen was taken before and after treatment with fluoride. The histomorphometric and histodynamic variables were compared (Table).

Discussion

In both children the natural history and bone radiology during extended treatment with corticosteroids for dermatomyositis seemed typical of corticosteroid induced osteoporosis. We could not study bone photon absorptiometry, but bone biopsy specimens were contributive: appreciable decrease of trabecular bone volume with decrease of the calcification rates and increased trabecular resorption

Table *Histomorphometric variables in bone biopsy specimens taken from the two cases*

		Trabecular bone volume (%)	*Resorption surfaces (%)*	*Osteoid volume (%)*	*Osteoid surfaces (%)*	*Thickness index of the osteroid seams*	*Calcification rate* (μ/day)
Case 1	Before treatment	9·8	6·3	7·6	34·6	21·9	0·84
	During treatment	10·0	15·3	10·5	48·2	21·7	1·76
Case 2	Before treatment	8·9	7·3	1·5	10·1	14·8	0·45
	During treatment	11·5	6·8	1·7	15·3	11·0	0·35
Controls (mean (SD))		22·9(4·5)	3·6(1·1)	2·1(1·4)	11(6·8)	19·3(3·6)	1·31(0·33)

Trabecular bone volume=percentage of trabecular bone tissue in total spongy space.
Resorption surfaces=percentage of total trabecular resorption surface area.
Osteoid volume=trabecular osteoid volume expressed as a percentage of total bone volume.
Osteoid surfaces=percentage of trabecular surface area covered with osteoid.
Thickness index of the osteoid seams=ratio of osteoid volume to osteoid surface area multiplied by factor of 100.
Calcification rate=calculated by double labelling of the calcification front with tetracycline.

surfaces are characteristic of adult corticosteroid induced osteoporosis.[3] Some criteria of diminished bone apposition (decrease in the thickness of the osteoid seams and increased osteoid surfaces), however, were seldom observed. Few data are available on corticosteroid induced osteoporosis in children, but it does not seem to be different from the adult disease.[4 5]

Curative treatment is still widely unknown. In a previous unpublished study we have shown that the use of calcium supplementation with alfacalcidol improved the calcium absorption in some cases but did not allow us to restore a sufficient bone mass or prevent new vertebral fractures. (Rejou F, Dumas R, Belon C, Meunier P J, Edouard C, Jean R. Bone histomorphometric studies compared with calcium absorption in juvenile corticoid-induced osteoporosis. Presented at European Society for Pediatric Research Annual Meeting, Cambridge, England, 16–20 September 1984.) Sodium fluoride is now an integral part of the treatment of idiopathic adult osteoporosis[1] and has been used in conjunction with calcium and vitamin D in corticosteroid induced osteoporosis.[2] In adults treatment with fluoride provides vertebral pain relief and irregular radiographic improvement. Histomorphometric studies reveal increases of trabecular bone volume, osteoid surfaces, and thickness index of the osteoid seams in most cases. The calcification rate has showed little modification when moderate doses of fluoride with calcium have been used in adult patients. The risks of treatment with fluoride are osteomalacia,[2] after a long course of treatment, joint pains, and digestive troubles. We did not observe such side effects in these two cases, but the treatment did not exceed two years. Clinical improvement and the absence of new vertebral fractures were observed, in spite of relapsing dermatomyositis in one case. Histomorphometric data after a year of treatment with fluoride showed inconsistent improvement: trabecular bone volume was unchanged and the calcification rate increased in one case. There is no evidence, however, that fluoride induced bone changes reflect an increase in mechanical strength.

We believe that treatment with fluoride together with calcium and alfacalcidol must be reserved for children presenting with severe corticosteroid induced osteoporosis. A bone biopsy examination with histomorphometric study seems useful in this situation. Further studies are needed to confirm these preliminary results.

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Infantile colic and feeding

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SUMMARY In a double blind crossover study 10 children with infantile colic were fed breast milk and cow's milk formula, untreated and treated with lactase. Colic was present on 71% of breast milk and 89% of cow's milk days. Daily duration and severity of colic did not differ for milk preparations.

Infantile colic, excessive and unexplained crying by healthy infants, commonly in the evenings, has been found to associate with cow's milk given as a formula[1] or used by the lactating mother.[2] In other studies no such associations have been detected[3 4] nor did infantile colic seem to be a symptom of lactose malabsorption.[5] To explore the connection between infantile colic and feeding we conducted a double blind crossover study using four milk preparations.

Patients and methods

Subjects. Ten weaned children, with a mean (SD) age of 11·9 (8·4) weeks, were referred to us by health nurses from well baby clinics because of infantile colic, which had continued since a mean (SD) age of 4·2 (7·0) weeks. On physical examination all children seemed healthy. Their mean (SD) weight gain since birth had been 216 (82) g per week. One child had asymptomatic bacteriuria without urinary tract anomalies. Urinary cultures of the other children yielded normal results. No pathogenic bacteria, rotavirus, or adenovirus antigens were found in faecal samples.

Milks. Four milk preparations were used in random order. These were (1) pooled breast milk; (2) pooled breast milk treated with Maxilact LX 5000 (Gist-Biocade, Delft, The Netherlands), hydrolysing enzymatically over 90% of lactose contents; (3) commercial adapted liquid cow's milk formula (Tutteli, Valio Ltd, Finland); and (4) the same cow's milk formula treated with Maxilact LX 5000 as above. Milks 2–4 were prepared, packed in coded cans, and delivered frozen by Valio Ltd. Untreated breast milk was frozen in similar coded cans. The aim was to feed each child for one week with each of the four milks. Frozen milk was given for one week's estimated need at a time. No other milk products were given to the babies during the study.

Recordings. The parents recorded daily the time, duration, and severity of attacks of colic. Once a week the children visited the clinic where they were examined, recordings from the previous week were returned, and milk for the next week was delivered.

Statistical methods. We used two way analysis of variance and Student's t test for analysis of data.

Results

Three children on cow's milk formula treated with lactase, one on breast milk treated with lactase, and one on breast milk had colic that was so severe that it was impossible to continue feeding for the planned time. None of the four milks differed significantly from the others in the percentage of days with colic (Table 1). Combining the milks into lactose containing and lactase treated groups showed no difference ($p>0·05$). Children had colic more often on cow's milk formulas (regardless of lactose) than on breast milk ($p<0·05$).

Table 1 *Days with colic/days on different milks in 10 patients with infantile colic. Roman numerals refer to the order of administration (I=first, II=second, etc)*

Case No	*Milk feed*			
	Breast milk	*Breast milk treated with lactase*	*Formula*	*Formula treated with lactase*
1	5/6 I	6/7 II	7/7 IV	7/7 III
2	3/7 III	1/3 IV	6/7 II	5/6 I
3	5/6 I	3/7 II	9/9 IV	5/5 III
4	6/6 I	6/7 II	7/7 IV	3/3 III
5	4/5 II	5/5 I	4/5 IV	5/5 III
6	1/7 IV	2/7 III	6/7 I	6/7 II
7	7/7 III	7/7 I	7/7 IV	3/3 II
8	4/7 I	1/7 IV	4/7 II	1/7 III
9	6/7 I	7/7 II	7/7 III	7/7 IV
10	3/3 IV	4/5 I	6/7 II	3/3 III
Total	44/61	42/62	63/70	45/53
Mean %	74·7	67·1	89·4	88·3

Two way analysis of variance: $F=2·958$, $df=3/27$, $p> 0·05$.
Student's t test: cow's milk formulas *v* breast milks, $p<0·05$; lactose containing milks *v* lactase treated milks, $p> 0·05$.

Table 2 *Duration and severity of colic: total hours with colic/No of symptomatic days (difficult colic in parentheses). The longest duration of each child is in bold*

Case No	*Milk feed*			
	Breast milk	*Breast milk treated with lactase*	*Formula*	*Formula treated with lactase*
1	0·6 (0·2)	3·4 (**3·2**)	**5·2** (1·6)	1·2 (1·0)
2	0·6 (0)	1·5 (0)	1·5 (0)	**2·8 (1·6)**
3	0·5 (0·5)	0·1 (0)	0·9 (0·7)	**3·8 (3·8)**
4	8·1 (7·3)	4·3 (2·5)	6·9 (3·3)	**17·0 (17·0)**
5	**5·2** (1·6)	4·6 (1·0)	0·8 (0·8)	4·3 (3·5)
6	0·2 (0·2)	0·2 (0·2)	0·1 (0·1)	**0·4 (0·3)**
7	1·5 (1·5)	1·1 (1·0)	1·0 (0·6)	**2·2 (2·2)**
8	0·7 (0·6)	2·0 (2·0)	**2·9 (2·9)**	1·8 (0)
9	**2·8 (0·8)**	1·5 (0·4)	1·9 (0·6)	1·2 (0·4)
10	**5·5 (5·5)**	2·7 (2·2)	1·2 (0·9)	3·5 (3·3)

Two way analysis of variance: F for overall colic=1·8, df=3/27, p>0·05; F for difficult colic=1·9, df=3/27, p>0·05.
Student's *t* test: cow's milk formulas *v* breast milks, p>0·05; lactose containing *v* lactase treated milks, p>0·05.

There were no differences between the milks in daily duration of colic (Table 2). Not even regrouping cow's milk formulas versus breast milks or lactose containing versus lactase treated milks showed any differences. Severity of attacks was also unaffected. In five children the total duration of colic and in six children the duration of difficult colic was, however, longest on cow's milk treated with lactase.

Discussion

The aetiology of infantile colic may be multiple, different causes operating in different children and perhaps one child's colic even being a result of several factors. To minimise the effects of confounding factors we conducted this investigation as a crossover study.

Colic was present on 89% of the days on cow's milk feeding and on 71% of the days on breast milk feeding. This difference was significant ($p<0·05$), but 71% is still high: colic is not cured by breast milk. No differences were found regarding severity of colic on those days when the disease was observed. Healthy infants may have physiologic lactase deficiency during several weeks,[6] but infantile colic is not a symptom of lactose malabsorption. Other factors than milk must be crucial.

We are grateful to Valio Ltd for donation of formulas and treatment of milks with lactase.

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Somatomedin C deficiency in Asian sisters

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SUMMARY Two sisters of Asian origin showed typical clinical and biochemical features of primary somatomedin C (SM-C) deficiency (Laron dwarfism). Abnormalities of SM-C binding proteins were observed, one sister lacking the high molecular weight (150 Kd) protein.

In 1966 Laron *et al* first described a form of familial dwarfism characterised by the clinical features of severe growth hormone (hGH) deficiency and high concentrations of plasma immunoreactive hGH.[1] Low plasma somatomedin activities before and during treatment with hGH indicate that the primary defect is in the production of somatomedin.[2] Most reported cases of this autosomal recessive disorder are in oriental Jews,[3] although a few patients of European origin have been described.[2] We report two Asian sisters with Laron dwarfism and describe abnormalties of somatomedin C (SM-C) binding proteins in their sera.

Patients

Case 1. This girl was born at term, weighing 2950 g, with a length of 45·0 cm (−2·5 standard deviation score (SDS)), to apparently non-consanguinous parents from Pakistan. The heights of both parents and three older male siblings were between the 25th and 50th centiles. She was 'jittery' shortly after birth, but hypoglycaemia was not confirmed. She grew poorly and at 2 years 3 months was referred to a paediatric endocrine unit. On examination her height was 67·5 cm (−5·6 SDS), weight 7·46 kg (−3·9 SDS), and triceps and subscapular skinfolds >97 centiles and she had typical somatic features of hyposomatotropism (Figure).

A full blood count, karyotype, tests of renal, hepatic, and thyroid function yielded normal results. Her bone age was 10 months. Serum prolactin concentrations rose from 112 mU/l to 1530 mU/l after intravenous thyrotrophin releasing hormone stimulation. Serum hGH concentrations ranged from 65 to 150 mU/l (mean 108 mU/l) during a 12 point 24 hour profile and from 54 to 100 mU/l (mean 80 mU/l) in an arginine provocation test. Serum insulin concentrations were <4 mU/l during arginine provocation.

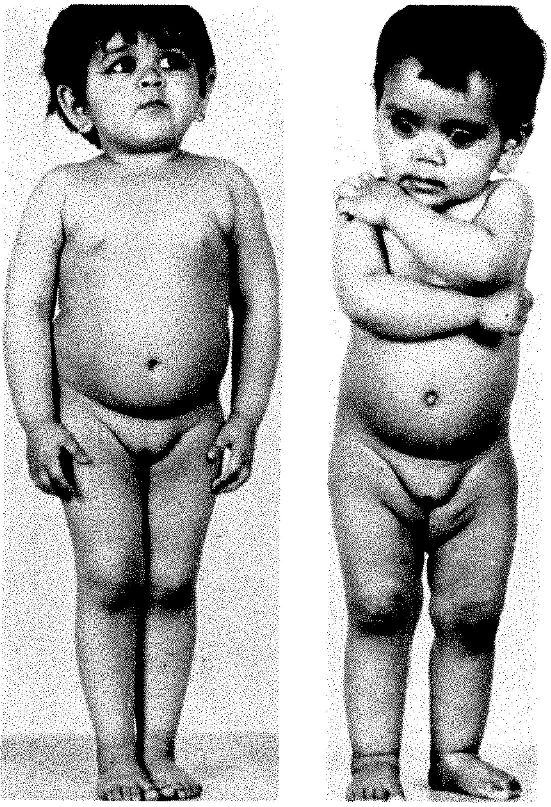

Figure *Case 1 (left) and case 2 (right).*

Before treatment with hGH, serum SM-C was 0·46 U/ml, serum somatomedin activity 0·32 to 0·45 U/ml during a 24 hour profile, and 24 hour urinary hydroxyproline/creatinine ratio 55; normal ranges at this age are 0·47–1·44 U/ml, 0·4–0·7 U/ml, and 45–204, respectively.

Serum binding of [^{125}I]Sm-C showed an absence of the specific 150 Kd binding protein and the presence of binding to proteins ranging from 20 Kd to 100 Kd, the greatest binding being of 40 Kd to 60 Kd.

After two weeks of treatment with hGH (4 IU intramuscularly three times a week) there was no increase in serum SM-C (0·2 U/ml), serum somatomedin activity (0·33 U/ml), and 24 hour urinary hydroxyproline/creatinine ratio (57). Despite a small increase in height velocity of 1 cm/year in the first month, this was not sustained over an eight month period.

Case 2. The sister of case 1 was born at 37 weeks' gestation with a weight of 3200 g, but her length was not documented. She had asymptomatic hypoglycaemia and early feeding difficulties. At 1 year her height was 61·4 cm (−5·1 SDS), weight 6·1 kg (−3·8 SDS), and triceps and subscapular skinfolds >97th centiles and she had typical features of hyposomatotropism.

Her karyotype and thyroid function were normal. Serum prolactin concentrations rose from 346 to 1400 mU/l after intravenous thyrotrophin releasing hormone. Serum hGH concentrations ranged from 45 to 135 mU/l (mean 91 mU/l) during a 12 point 24 hour profile and from 35 to 120 mU/l (mean 64 mU/l) during an arginine provocation test. Serum insulin concentrations were <4 mU/l during arginine provocation. Basal serum SM-C concentrations ranged from 0·12 to 0·23 U/ml (mean 0·18 U/ml) and basal serum somatomedin activity from 0 to 0·37 U/l (mean 0·16 U/l).

Serum binding of [^{125}I]SM-C showed the presence of the specific 150 Kd binding protein and small amounts of binding activity at higher and lower molecular weights, especially in the 40–60 Kd region.

Methods

hGH was measured by double antibody radioimmunoassay and somatomedin biological activity by the porcine costal cartilage bioassay. SM-C was measured by radioimmunoassay as previously described[4] after the removal of somatomedin binding proteins by extraction with acid-ethanol. The somatomedin binding proteins themselves were detected by their competition with activated charcoal for $[^{125}\text{I}]$SM-C, as previously described,[4] after the fractionation of serum on Sephadex G200 eluted with 0·05M phosphate buffer.

Discussion

The clinical and biochemical features of these two sisters strongly support the diagnosis of primary somatomedin deficiency, which was confirmed by failure of response to treatment with hGH in the older child. hGH injections did not produce somatomedin generation, although the small increase in height velocity, which has also been reported in other cases,[1 2] led us to continue the therapeutic trial for eight months. It was not considered appropriate to offer treatment to the younger sister.

Circulating SM-C (insulin like growth factor 1), with its binding proteins, may predominantly reflect paracrine activity in growing tissues, have a true endocrine role, or represent the sum of paracrine and endocrine activity. SM-C is known to be hGH dependent in normal individuals, however, and is characteristically deficient in Laron dwarfism, despite high concentrations of endogenous hGH or treatment with exogenous hGH. SM-C does not exist in a free form in the plasma but is bound to proteins of various molecular weights, including a specific large molecular weight carrier protein (150 Kd) that is itself hGH dependent and may be a hexamer of subunits of 24 Kd.[5] An additional 40 Kd binding species is present in various body fluids but is not dependent on growth hormone. The 150 Kd protein was absent in the older sister but present in the younger. It has been suggested that Laron dwarfism is due to defective hGh receptors;[6] thus heterogeneity of production of the hGH dependent 150 Kd protein is puzzling and may reflect quantitative differences of receptor number. This warrants further study.

The occurrence of Laron dwarfism in an Asian family should alert clinicians to consider the possibility in other Asian children with extreme short stature, relative adiposity, and high circulating hGH concentrations. Other features may include shortness at birth, neonatal hypoglycaemia, and a characteristic and appealing 'babyish' face with small central facial structures, relatively large calvarium, and occasionally a 'surprised appearance' due to slight proptosis. Hypogenitalism is noticeable in boys with this disorder. The condition is rare and is more likely to occur in a population with a high degree of consanguinity. It is hoped that in the future a trial of SM-C treatment may be of benefit.

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$[^{125}\text{I}]$SM-C and SM-C antibody (AS6) were kindly provided by Drs J J Van Wyk and L E Underwood, University of North Carolina, through the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases.

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Personal practice

Neonatal opiate withdrawal

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The Problem

With increasing maternal drug abuse, the paediatrician must be ever alert to the possibility that symptoms observed in a young baby might be the consequence of drug withdrawal. The absence of a positive maternal drug history in no way negates this diagnostic possibility. Although opiate withrawal is the subject of this paper, combinations of drugs are commonly involved and there may sometimes be little certainty concerning the identity of the principal agent causing a given baby's withdrawal symptoms.

Mechanism of opiate withdrawal

Excitation of noradrenergic cells in the locus coeruleus of mammals elicits many of the features of opiate withdrawal. Morphine and clonidine, an alpha$_2$ adrenergic agonist, are inhibitory and block both electrical and pharmacological activation of these cells in primates and rats.[1] [2] Chronic exposure to morphine in rats results in the development of an increase in number of brain stem alpha$_2$ adrenergic binding sites,[3] and it is postulated that the phenomena associated with opiate withdrawal are the consequence of the development of alpha$_2$ adrenergic supersensitivity; this can be suppressed by clonidine.

Signs of withdrawal

Behavioural and physical modalities reflecting central and autonomic nervous system dysfunctioning are involved. Features of neonatal abstinence include restlessness and agitation with rub marks, a high pitched cry, sleeplessness, tremulousness, hypertonia, hyperactive stretch and Moro's reflexes, frantic sucking, scratching, impaired feeding with poorly organised sucking, vomiting, diarrhoea, abnormal weight loss and failure to gain weight, yawning, sneezing, nasal snuffles, sweating, temperature instability, tachycardia, hypertension, tachypnoea, opisthotonic posturing, and convulsions.

Some of these signs are observed in many neonatal conditions. Drug withdrawal must be considered, however, as a possible cause when several occur concurrently and in increasing numbers.

Timing of onset of withdrawal

If the fetus has been exposed to several drugs up to the time of birth the onset of symptoms may be variably delayed beyond the usual first three days. Although methadone has been implicated in the late onset of the signs of withdrawal, when appropriately monitored, all reported cases have manifested some signs within the first two weeks; with polydrug exposure a biphasic pattern of withdrawal has been described.[4] Administration of naloxone at birth is contraindicated as it may precipitate acute withdrawal, which could be fatal.

Diagnosis

This must be by exclusion of other possible disorders and by obtaining a positive history of maternal ingestion. Alternatively, drug or metabolite may be found in maternal blood or urine or in neonatal urine or meconium.[5]

Principles of treatment

Awareness of the drug abuse may have come antenatally from a mother's own admission or from clinical or social evidence. Prospective monitoring of the infant on a special care baby unit will then be possible. The objectives of treatment are the suppression of signs, the avoidance of excessive sedation and of excessive wakefulness, and the provision of sufficient nutrients. It has been suggested that in 30–50% of infants symptoms of withdrawal can be managed conservatively with swaddling, frequent small hypercaloric feeds, and intravenous fluids when necessary. Prediction of immediate outcome is improved by pharmacological intervention, although assessment of the progression of withdrawal severity is useful as a guide both in the timing of the introduction of treatment with drugs and in evaluating the response. A scoring system of withdrawal signs, although subjective and dependent on observer experience and bias, is one approach to meet these objectives (Figure).

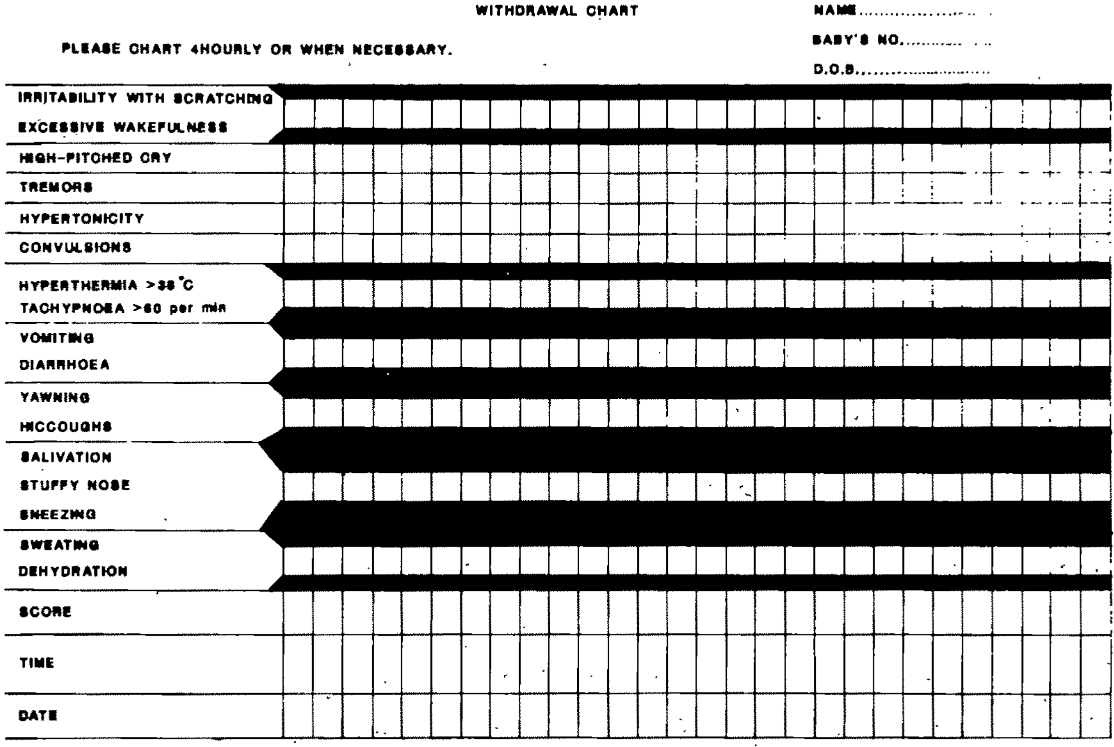
Many factors, including sources of health funding and the availability of post-discharge support facilities, may affect treatment policies as pharmacological intervention usually results in a longer period of admission to hospital; this is particularly so where it is policy not to discharge a baby while still receiving treatment with drugs.

Pharmacological intervention

The most commonly used agents include paregoric, tincture of opium, diazepam, phenobarbitone, and chlorpromazine; these have been reviewed by the American committee on drugs.[6] Although opiates, diazepam, and phenobarbitone are widely used in the United States, chlorpromazine has tended to be the preferred treatment in the United Kingdom. Diazepam and phenobarbitone are more likely to produce undesirable sedation and they do not control the gastrointestinal or nasal features of withdrawal. The snuffly nose and sneezing are also little affected by chlorpromazine. Clonidine has been used successfully in treating adult withdrawal[7] and has been used in neonatal abstinence,[8] although, as yet, there is little published experience of its use. Complications of phenothiazine usage have been notably absent, although rarely seizures can occur, and at a time when other symptoms of withdrawal are under control. It remains to be established whether chlorpromazine itself, or withdrawal from some other drug—for example, a barbiturate—is the cause of seizures in these babies.

Associated infections

The hepatitis B e antigen state and human im-



WITHDRAWAL CHART

PLEASE CHART 4HOURLY OR WHEN NECESSARY.

NAME..................

BABY'S NO..............

D.O.B...................

IRRITABILITY WITH SCRATCHING
EXCESSIVE WAKEFULNESS

HIGH-PITCHED CRY

TREMORS

HYPERTONICITY

CONVULSIONS

HYPERTHERMIA >38 °C
TACHYPNOEA >60 per min

VOMITING
DIARRHOEA

YAWNING
HICCOUGHS

SALIVATION
STUFFY NOSE
SNEEZING

SWEATING
DEHYDRATION

SCORE

TIME

DATE

Figure *Score chart for withdrawal signs. The presence of any one feature within any group of the listed observations would result in a total score of 1 for that group of items. The total score possible is therefore 10. Treatment is likely to be required for any score of 6 and over or for convulsions.*

munodeficiency virus (HIV) antibody state of the mother should be known before labour, but where the results have been negative in pregnancy, or when they are not known, rapid evaluation is needed on admission of the mother for delivery. This knowledge not only enables precautions to be taken to protect staff and other contacts but enables hepatitis protection to be given to the neonate in the form of specific hyperimmune globulin and active hepatitis B immunisation. Before HIV screening, counselling of the pregnant mother by a trained counsellor about the implications of a positive result is considered essential.

Breast feeding

Although breast feeding has often been discouraged because of the concern of drug ingestion by the infant, we could only find trace amounts of drug in the milk of a group of mothers taking methadone and heroin. In our experience it would be exceptional for large dose intravenous drug abusers to be successful at breast feeding and so we do not dissuade mothers from feeding their infants, although HIV antibody positivity would be a contraindication. Perhaps the greatest danger of drug exposure from breast feeding is in the situation of the mother who is an occasional intravenous abuser, because high drug concentrations in the blood may sedate her and make her less responsive to and appreciative of her baby's needs as well as being reflected in a higher concentration of drug in her breast milk.

Legal provisions for the child at risk

As yet it is not possible to seek protection for a fetus from the juvenile court or by taking wardship proceedings on the basis of the assertion that the fetus is being damaged by the mother's drug abuse. Postnatally, both options have their shortcomings in providing for these children and their families, and the proposed reforms set out in the Review of Child Care Law 1985,[9] if adopted, may provide for a more flexible approach to their needs. The difficulties arising from the current alternatives have been discussed by Williams.[10]

Supervision

Many of the problems of long term family supervision considered recently in connection with children subject to non-accidental injury[11] are equally applicable to children raised in drug abusing families, and in spite of apparent cooperation with the authorities, many addicts fail to achieve, or do not desire, a change in lifestyle, and family supervision cannot be relaxed.

Our own follow up data on families with babies born between 1968 and 1983 show that of 85 babies leaving hospital and traced only 25% were living with both parents, 20% were with their mother, and 12% were with their father. A further 36% were with other relatives, had been adopted or fostered, or were in other placements. Six parents and four children had died. (Williams M J H, Cavanagh S. Personal communication.)

Outcome

Differences between control and drug exposed groups of children have been documented by many investigators and have been the subject of a recent review.[12] Strauss *et al* found them to be more tremulous at a month;[13] Marcus *et al* have shown patterns of behaviour characteristic of acute phase opiate withdrawal at a similar age.[14] There are considerable difficulties, however, in selecting any comparison 'control' groups. Rosen *et al* found that in a group of methadone exposed children examined at 18 months of age, more had head circumference measurements below the 3rd centile, developmental delays, abnormalities of tone, and poor fine motor coordination.[15] Significantly lower scores on Bayley mental and motor developmental indices were noted.

Although there are minor differences between studies, the overall impression is that these children perform less well, are more active, and display poorer attention then their peers. There are few follow up data on older drug exposed children; such as they are, they point to persisting disadvantage, with behavioural and developmental skill differences.[1]

A proposal for management

After an antenatal case conference where information is exchanged, a strategy for the health care of the family during the perinatal period is formulated and the principal family support individuals are identified so that contact, if not previously existing, can be made with the family. The baby, once born, would be monitored for withdrawal symptoms on a special care baby unit for two weeks. If treatment with drugs is necessary to control withdrawal chlorpromazine is begun with a loading dose of 3 mg/kg body weight followed by a total daily maintenance schedule of 3 mg/kg given orally, divided into four or six doses; this dose is increased daily by 3 mg/kg if withdrawal is becoming increasingly severe until control is achieved.

Occasionally, as much as 15 mg/kg each day is required. Once the baby's condition is stable, reduction in chlorpromazine dosage by 2 mg/kg is attempted every third day; monitoring of the degree of withdrawal symptomatology is continued. Excessive weight gain with high feed intakes is often observed in association with control of symptoms being achieved, whereas slowing or stopping of weight gain due to the rise in metabolic rate occurs if uncontrolled opiate withdrawal re-emerges. After stopping treatment with chlorpromazine a further case conference is held where the need for obtaining legal protection for the child is further considered and a plan made for follow up visits after discharge by social workers and health visitors. Before discharge, the baby and mother are cared for together on a transitional care or postnatal ward for a 'rooming in' period of three or more days. A review case conference is held at three months after the first hospital outpatient follow up visit, when decisions are made on the level of involvement deemed necessary and the frequency of subsequent conferences. At any stage, procedures may be set in motion to seek a care order on the child or to obtain wardship. The lifestyle of many of these families makes continued tracing and contact a major collaborative undertaking.

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Archives of Disease in Childhood, 1986, **61,** 1240–1241

Tracheostomy—a parent's view

When we were first told that Michelle was going to have a tracheostomy performed I cried in the car on the way home from the hospital. As a staff nurse, I remembered the stigma that a tracheostomy held and how we used to dislike nursing one. How we were going to cope with a young baby with spina bifida and a tracheostomy I could not imagine. All my husband and I did know was that we loved our daughter very much.

At first when she came home, we were very apprehensive that the tracheostomy tube would block with secretions, as they had blocked twice before when she was in hospital. For the first few days and nights I hung wet towels around her cot and kettles steamed constantly (the house began to look like a combination of a Chinese laundry and a Turkish sauna!).

Within a couple of days, I realised that these drastic measures were not necessary as the atmosphere at home was more humid than in hospital. Only when the weather was very dry and Michelle's secretions became very thick was it necessary to humidify the air slightly.

Michelle was a very difficult feeder, despite enlarging the holes of the teat, and winding frequently she would often cough and bring up the whole feed. At one stage she was so bad it was necessary to feed her with a bowl in front of me to catch the vomit when she coughed. (It helped that whenever possible my husband would feed Michelle for me; this helped us to relieve a lot of the tension.) Michelle was also very slow starting her solid diet. She seemed to show difficulty in the actual swallowing mechanism and would often 'gag'. But at 1 year she was taking her solids well and at long last was keeping her feeds down when she coughed.

When she began to use a cup for drinking we had to take great care that her 'dribbles' did not trickle down into her colostomy, making her cough. When she began feeding herself it became a fight to get to her tracheostomy without grabbing the suction catheter and getting food all over it. With practice one became the 'fastest aspirator in the west'.

When Michelle first came home, she required suction a lot and was a full time occupation. (As we only aspirated the top of the tracheostomy tube and did not enter her lungs we used a larger suction catheter (8 gauge instead of 6) with a low pressure of 200 mmHg we were able to aspirate mucous and keep the tracheostomy tube hole patent). In hospital tracheostomy aspiration is a sterile technique in which gloves are worn and the catheter discarded after use. At home it became a clean technique only but it did not seem to matter.

Michelle was with us every minute of the day; she would sleep downstairs with us until it was time to go to bed and would be carried to her cot by our bed when we retired for the night.

The first few nights Michelle was at home we hardly slept but very quickly learned to adapt to sleeping lighter than usual so that we could hear if Michelle required suction. While asleep, she did not require suction as her respirations were lighter, but waking she would make a little 'rattling' noise from her tracheostomy, which meant she needed suction. If you pretended to be asleep she found out that playing with the beads on her cot attracted our attention. Michelle accepted her tracheostomy as being part of herself and would make attempts to aspirate herself, frequently asking for suction if she felt she needed it. Michelle would often explore her tracheostomy with her fingers; although it made us anxious at times, we never discouraged her as we felt it was perfectly natural for her to be curious.

The suction machine became a very important part of our lives, and visiting became a massive task, with the transport of catheters and 'baby things'. The suction machine was usually cleaned out once a week when Michelle was asleep. When the tracheostomy eventually closed it was only when I gave the machine back to the local authority that I felt that Michelle would no longer need to have a tracheostomy (the feeling is hard to explain). We were provided with a portable suction machine as well as an electric one. This was a godsend as it meant we were able to go out with Michelle and we were no longer prisoners in our own home. Michelle loved going around the shops, especially the supermarket. At first it was a little embarrassing as people were naturally curious about what we were doing when we went to aspirate her. From the very start we forced ourselves not to retreat into a dark corner as if we were doing something terrible. With time we learnt to come to terms with people's curiosity and found people could be very kind, though it took courage and determination to have a meal in a crowded restaurant. Children surprisingly accepted Michelle's tracheostomy more easily than adults.

When 8 months, we went on holiday to Cornwall in a caravan for a week, with just the portable suction machine. It was hard work pedalling the suction machine, but having a holiday was tremendous and we all enjoyed the break.

When we went away on holiday, strangers would remark on what a good baby we had as they had never heard her cry at all during the night. I worried that she would become frustrated not being able to tell us what she wanted or needed. She was further hindered by being a spina bifida child and therefore less mobile. Michelle became very clever, however, at using body and facial language to relay her needs—for example, pointing with her finger, rubbing her eyes to say she was tired, or moving the back of her hand over the tube, meaning she wanted suction. This is where Michelle first gained from being at home as we learnt to understand her language and interpret her needs.

Bathtime was a joy for Michelle, and the water held no fear for her. We used to lie her on her back in the water (keeping her tracheostomy above water level!). Any water that trickled down or was splashed down into her tube she was able to expectorate easily, before it went far into her lungs.

We soon got in to the routine with the everyday care of the tracheostomy. Around the tube the skin would be cleaned twice a day with cooled boiled water and cotton wool. I never used sodium bicarbonate solution as I found it too irritating for Michelle's skin. For a barrier cream we found a combination of Drapolene then Sudocrem kept the skin in good condition. As Michelle grew older she would help in the care of her tracheostomy, by helping to rub the cream in. In hot weather, when Michelle used to perspire more, she did sometimes get a rash where the tapes were. We found by rubbing a small amount of Timodine into the affected areas, twice a day, then dusting over with a thick layer of talcum powder to set the cream the rash would disappear within a couple of days.

Michelle's tapes would be changed about once every three days depending on how dirty they were, and from an early age, before changing her tapes, we would always tell her what we were going to do and make a game of it. When we first began to change her tapes we found it very frightening and Michelle would sense our apprehension and would cry and become anxious. We overcame this by using an unorthodox method of tying the new tapes on while the old tapes were still in situ. The correct tension was obtained when the index finger on the left hand could just be placed underneath the tapes while the head was flexed backwards. The old tapes were then cut off. Despite being told by countless people that Michelle's little hole would not seal itself when her tracheostomy tube was removed, it was only when we saw it for ourselves were we truly at ease with looking after Michelle's tracheostomy.

We used to dread the winter coming as with it would come the chest infections. I could not help but blame myself and think that each chest infection reflected some failure in my care of Michelle. We were very lucky in that we had a good back up system of understanding receptionists and doctors who would see Michelle whenever we were worried about her condition. Michelle was fortunately a very good patient and we were able to nurse her when she was ill with chest infections.

To relieve the tension that the parents of children who have tracheostomy's feel there is a definite need for a back up system of nurses who are able to baby sit for the parents and give valuable time in which the husband and wife can be alone together. It is unfair and often impossible to expect close family to baby sit as they often feel the responsibility too great and too stressful.

There were times when we wondered how we were going to carry on, but we realise that it would only be a short period that she would be very demanding and that the rewards of having her home with us far outweighed the inconvenience. The constant care and love she was able to receive from being home helped her to become emotionally stable and progress much quicker than she would have done in hospital.

(Michelle was the first child of a family living in north Wales. She was born with a meningomyelocele at lumbar 2/3 level, which was closed, in Liverpool, on the second day. Hydrocephalus developed and also severe stridor one month after birth, which did not improve despite a shunt for the hydrocephalus. The tracheostomy was performed at 10 weeks of age and was required until Michelle was 2½ years old, at which time it could be closed. Michelle is now 6 years old and attends a school near her home—ed.)

Archives of Disease in Childhood, 1986, **61,** 1242–1247

Correspondence

As an exception to our policy we are publishing the following long letter, which deals with a complicated topical issue.

Immunoprophylaxis of infants born to hepatitis B virus exposed mothers

Sir,

In recent correspondence Drs Ewing and Davidson suggest the limited supply of specific hepatitis B immunoglobulin as the only reason for the restriction of hepatitis B immunisation of infants in Britain to those whose mothers are negative for antibody to hepatitis e antigen (anti-HBe).[1] The decision to limit hepatitis B immunisation to this group, in the first instance at least, was based, however, not only on the immunoglobulin supply but on risk, benefit, and cost assessments, of which only parts have been published.[2 3] In view of the concern that may be aroused by the report of fulminant hepatitis B in an infant of an anti-HBe positive mother in Britain, a more detailed account of these assessments is given below.

The prevalence of anti-HBe positive and hepatitis B surface antigen (HBsAg) carriage in Britain

Estimates—based on country of birth and the rates of HBsAg carriage and anti-HBe positivity expected in various ethnic groups—suggest that in Britain about 2000 infants are born annually to carrier mothers, about four fifths of whom are anti-HBe positive: less than 400 of the carrier mothers are white but a larger portion of them, about nine tenths, are anti-HBe positive.

The risk of perinatal exposure to anti-HBe positive mothers

The number of virus particles per millilitre in the serum of anti-HBe positive carriers is small, so that most infants born to these mothers escape infection completely, but about 10% have transient symptomless infections with subsequent development of immunity.

Acute hepatitis did not occur as a problem in prospective studies, but there have been a few published reports, including one from Britain, of severe hepatitis B in the first months of life in infants of carrier mothers, some of whom were anti-HBe positive.[4–6] The reports cannot indicate, however, the incidence of the illness. A rough assessment of incidence in Britain can be made on the basis of routinely collected data—that is, statutory notifications, death certificates, and Public Health Laboratory Service (PHLS) Communicable Disease Reports.

Notifications of infective jaundice

Notifications do not give a complete account of the incidence of clinical infections but they are reliable indicators of trends. Annual fluctuations in notifications of infective jaundice are known to depend upon the incidence of type A infection rather than type B, which tends to remain at a low, fairly constant level. There are few notifications of infective jaundice for infants of less than a year and the trend in the period 1968–81 corresponds well with that of all notifications,[7] suggesting that when acute hepatitis occurs in infants it is usually type A (Table 1).

Death certificates

Office of Population Censuses and Surveys reports of deaths from viral hepatitis.

In the seven years 1975–81, 10 infants aged less than 1 year died of viral hepatitis: of the 10, six were 6 months or less. The type of infection was not stated (this is not a requirement), but a negative HBsAg test was recorded for one of the six and another died at three weeks, earlier than a type B infection would be expected to manifest.

PHLS Communicable Disease Reports of acute hepatitis B

These reports of acute hepatitis B confirmed by laboratory tests seem to provide an estimate of incidence as reliable as that of a population study.[8] In any event it is expected that an illness as uncommon in an infant as acute hepatitis would be investigated thoroughly, including serological tests, the results of which are expected to be reported to the communicable disease report routinely. During the seven years 1975–81, seven infants with HBsAg positive illnesses and one other infant positive for antibody to hepatitis surface antigen (anti-HBs) were reported. Five of the HBsAg positive and the one anti-HBs positive illnesses were in the first six months of life. None of the infants was reported to have died, and this was confirmed by inspection of the death certificates.

Table 1 *Notifications infective jaundice*

	Year												
	1969	*1970*	*1971*	*1972*	*1973*	*1974*	*1975*	*1976*	*1977*	*1978*	*1979*	*1980*	*1981*
Total	23580	21584	14142	12269	8073	7620	5756	5954	5123	4673	3216	5143	9834
Age <1 year	26	21	18	10	13	16	13	9	9	7	4	7	10

Table 2 *Approximate cost estimates for various options in hepatitis B prevention*

Option	*Approximate annual cost (£)*
Selective screening of antenatal patients:	
(i) Antibody to hepatitis B immunoglobin (Anti-HBIg) at birth plus hepatitis B vaccine for infants of 'high risk' mothers: no immunisation for infants of anti-HBe positive mothers	46000
(ii) Anti-HBIg at birth plus hepatitis B vaccine for all infants of HBsAg positive mothers	151000
Screening of *all* antenatal patients:	
(i) Anti-HBIg at birth plus hepatitis B vaccine for infants of 'high risk' mothers: no immunisation for infants of anti-HBe positive mothers	120000
(ii) Anti-HBIg at birth plus hepatitis B vaccine for all infants of HBsAg positive mothers	246000

It is emphasised that these assessments apply to Britain only. Acute hepatitis B can be expected to be more common among young infants in populations with higher HBsAg carrier rates.

The mothers of the five HBsAg positive infants were reported to be HBsAg positive, but results of HBe antigen and antibody tests were not recorded.

According to these reports, in Britain each year less than one infant develops acute hepatitis B as a result of perinatal exposure. On this basis, it would be necessary to immunise more than 2000 neonates of anti-HBe positive mothers to prevent acute hepatitis B in one young infant. More recent Communicable Disease Reports confirm this assessment. Since the surveillance began in 1982 more than 5000 infants are estimated to have been born to anti-HBe positive carrier mothers in Britain: during this time there have been only two reports of acute hepatitis B in early infancy, including the infant who died.

Cost estimates of various options

A summary of estimates made in 1983 is given in Table 2. These do not include the cost of salaries of clinical and laboratory health service staff. A reduction in expense due to the recent introduction of paediatric doses of hepatitis B vaccine will have been offset by increases in other costs—for example, laboratory tests—since 1983.

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Ethical aspects of neonatal care

Sir,

Dr Bissenden's annotation on 'Ethical aspects of neonatal care'[1] is based on a series of (conceivably false) premises that render illogical his conclusion that each case should be treated 'without preconceived ideas'. All our decisions are influenced by some underlying moral reference points and I for one would totally reject several of those on which Dr Bissenden's decisions are based. What is the evidence that life clearly does not begin at the fusion of the gametes? When does it begin? At 40? At what stage in infancy does one become a child thereby acquiring rights? (The United Nations Declaration of the Rights of the Child of 1959 includes the phrase 'before as well as after birth'.) Has the author never observed the two way communication between parents and their severely handicapped child 'of mental age no more than 2'? To label as evil someone who supports the life of a severely handicapped child is to make a highly offensive value judgment, presumably based on Dr Bissenden's idiosyncratic definition of good and evil. At the same time the Catholic position is conveniently dismissed by simply avoiding it.

There is no doubt that we are facing many taxing ethical problems in neonatal practice. It would be most unfortunate if Dr Bissenden's philosophy was to become the basis for solving them.

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Dr Bissenden comments:

The inevitable consequence of writing on a subject such as 'Ethical aspects of neonatal care'[1] is that whatever one writes someone will strongly disagree. There is no reason to believe that doctors will have uniform moral reference points relevant to an issue, any more than teachers or lawyers will.

Dr McGucken asks difficult questions, provides no answers, and is very critical. His beliefs, however, are highly personal. They should be respected but are as irrelevant as mine. I do not have an absolute view on the subject, but what I tried to do in the annotation was to acknowledge that most neonatologists in the United Kingdom were, under certain circumstances, withdrawing intensive care from premature neonates. That being the case, when examining the logistics of decision making, and considering the criteria involved, one cannot avoid this thorny problem of the quality of life.

If Dr McGucken accepts that he faces taxing ethical problems in neonatal practice, then he must have some concept of a life so awful and so full of misery that it would be morally wrong to support it intensively. It is merely a matter of an alternative definition. I cannot believe that because of the experience of rewarding relationships between parents and their handicapped child he thinks life should be preserved whatever the cost.

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Serum albumin concentrations and oedema in the newborn

Sir,

The paper by Cartlidge and Rutter contains much valuable information on albumin concentrations and oedema in the preterm neonate.[1] Early (<7 days) oedema does not usually cause undue concern if attention is focused on fluid and electrolyte balance as part of the overall care at that stage.

It is the occurrence of later oedema in the relatively well, rapidly growing preterm baby that is the more interesting physiological (?) phenomenon, even if it is the less worrying clinically. The authors reported a significant relation between albumin concentration and oedema, but with a poor correlation. No relation between nutritional state and albumin concentrations existed at 3 weeks of age. Which measures of nutritional state were used to support this statement?

It is tempting to find similarities between this late neonatal oedema and some forms of nutritional oedema. The role of protein deficiency and secondary hypoalbuminaemia as the principal cause of oedema in kwashiorkor has been questioned.[2 3] Some malnourished children develop oedema during nutritional recovery at a time when their albumin concentrations are rising.[4]

If these phenomena are paralleled in preterm babies oedema and hypoalbuminaemia in the late neonatal period may reflect nutritional inadequacies. Dismissal of the nutritional state, particularly if assessed by anthropometry alone, may be premature. Thus the excellent data presented should encourage us to look for nutritional problems rather than dismissing them.

Eventually, only meticulous balance studies on energy, protein, and 'accessory nutrients'[3] may lead to an understanding of which, if any, of these dietary factors is deficient in the growing baby with oedema. It would be interesting to know whether Drs Cartlidge and Rutter found hypoalbuminaemia and oedema (independently) to be related to previous nutrition in these babies. Did the type of milk used or the parenteral route of feeding have any influence on the incidence of these problems?

Michael Watkinson
Marston Green Hospital,
Birmingham B37 7HS

Sir,

The recent paper by Cartlidge and Rutter is an important objective attempt to try to find whether hypoalbuminaemia is a cause of oedema in the preterm infant.[1] The study oversimplifies the problem and cannot justify the conclusion that plasma albumin measurement in preterm infants is not helpful. The causes of oedema in an acutely ill infant with severe respiratory distress are likely to be different from those in an infant several weeks old requiring total parenteral nutrition. Did the authors analyse such groups separately? Plasma albumin is just one factor influencing oedema formation; others include fluid intake, fluid output, and capillary leakiness. If a low plasma albumin concentration is found in conjunction with oedema plasma albumin concentration is one factor that can be influenced. In my experience oedema in babies of more than 2 weeks of age with a plasma albumin concentration of less than 20 g/l often respond to an albumin infusion with a loss of oedema. I would therefore suggest that measurement of plasma albumin concentration should not be abandoned as suggested by the authors.

P W Miller
St Mary's Hospital,
Manchester M13 0JH

Drs Cartlidge and Rutter comment:

We agree with Dr Miller that the cause of oedema in the two situations he cites is likely to be different; we found no correlation, however, between oedema and hypoalbuminaemia in well and ill infants during both the early and late neonatal periods. As the mean arterial blood pressure is lower in preterm infants than in adults it is likely that capillary hydrostatic pressure is also considerably less. It is therefore not surprising that the preterm infant can tolerate hypoalbuminaemia without becoming oedematous. In view of this, we find Dr Miller's experience with albumin infusions surprising. Indeed, if capillary leakiness is important in oedema formation as he suggests the albumin given would merely leak into the interstitial fluid and oedema may thereby be increased.

Dr Watkinson makes an interesting suggestion, which links late onset oedema to poor nutrition. The nutritional state of 3 week old infants in our study was determined by their weight. They were divided into three groups depending on whether their weight was less than 95%, between 95% and 105%, or more than 105% of their birth weight. There was no significant difference in serum albumin concentration between these groups. Oedema was not influenced by the type of nutrition received, but serum albumin concentrations tended to be lower in those infants fed parenterally.

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Haemophilus influenzae type b meningitis resistant to ampicillin and chloramphenicol

Sir,

Guiscafre *et al* have reported two cases of meningitis due to *Haemophilus influenzae* type b resistant to ampicillin and chloramphenicol.[1] In their report they say 'since 1980 eight cases of meningitis. . . have been reported'. This is not true. In previous reports we have drawn attention to the explosive increase of multiply resistant strains of *H. influenzae* type b causing invasive and non-invasive infections in Spain.[2] [3] From January 1981 to December 1984 we have seen over 364 consecutive cases of culture proved bacterial meningitis, 35 of which (9·6%) were caused by *H. influenzae* type b. In 20 cases (57%) strains were found to be resistant to ampicillin and chloramphenicol.

As this problem has also been described in other parts of Spain we are led to the conclusion that in our country resistance of *H. influenzae b* to ampicillin and chloramphenicol could be endemic. Uncontrolled and widespread use of antibiotics in Spain over many years played a role in the emergence of these multiply resistant strains.

We cannot use ampicillin and chloramphenicol as initial treatment of meningitis caused by *H. influenzae b* and we are currently using cefotaxime as the treatment of choice until susceptibility tests become available.

The report from Mexico, like others, remind us of the possibility of emergence of strains resistant to both antibiotics in every country.

J M Gairi, J Campos, *and* S Garcia-Tornel
San Juan de Dios Children's Hospital,
Barcelona, Spain

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High plasma urea concentration in babies with lamellar ichthyosis

Sir,

The interesting observation of Beverley and Wheeler about raised plasma urea concentration after cutaneous application of Calmurid (10% urea and 5% lactic acid) in collodion babies or in babies with lamellar ichthyosis was attributed to increased urea absorption through the skin.[1] This explanation seems logical. There are two additional factors that may contribute, however, to the rise in plasma urea in these patients: (a) the application of a hygroscopic substance like urea can increase the hydration of the skin[2] but may decrease the water contents of other tissues, and (b) babies with lamellar ichthyosis have a tendency towards dehydration caused by increased loss of water through the affected skin. My colleagues and I reported several babies with lamellar ichthyosis who developed hypernatraemic dehydration due to excessive loss of water through the skin.[3] They were not treated with urea cream but developed raised serum urea on several occasions in association with hypernatraemic dehydration, as can be seen from the examples in the Table.

Table *Urea concentrations in three cases of lamellar ichthyosis who developed hypernatraemic dehydration*

Case No	*Age (days)*	*Weight loss*		*Plasma urea (mmol/l)*	*Plasma sodium (mEq/l)*	*Plasma chloride (mEq/l)*
		(g)	*(% Of body weight)*			
1	3	490	11	10·0	159	118
2	42	160	7	9·6	165	120
3	91	165	7	9·6	158	126
	334	140	5	29·9	179	151

The state of hydration of babies with lamellar ichthyosis can be difficult to evaluate as the skin turgor is not a reliable sign of hydration. The amount of water loss through the skin in lamellar ichthyosis is variable and probably depends on the condition of the skin; shedding of the scales, with exposure of great areas of erythematous skin can increase the insensible water loss, although aesthetically the skin appears improved. Thus dehydration can be a relatively common cause of rises in plasma urea concentration in babies with lamellar ichthyosis.

B Z Garty
The Children's Hospital of Philadelphia,
Philadelphia,
United States of America

Drs Beverley and Wheeler comment:

We read with interest the comments of Dr Garty and agree with him that other factors may have contributed to the raised plasma urea in our patients, particularly in case 1 who had lamellar ichthyosis. We were able, however, to observe case 2 (whose underlying skin was normal) more closely. She had normal plasma creatinine concentrations at the time of the raised plasma urea concentration (as shown in the Figure of our paper[1]), her weight never fell more than expected for a newborn infant, the plasma urea fell on stopping treatment with Calmurid, and throughout she maintained a good urine output. These factors suggested to us that the primary cause of the raised urea was transdermal absorption of urea rather than dehydration as suggested by Dr Garty. Because of our experience with case 1 we felt it to be inappropriate to challenge case 2 with further treatment with Calmurid to determine whether the plasma urea would rise again. The patients that Dr Garty describe are of interest; again making the point that skin, in particular abnormal skin, is not an impermeable barrier, in his cases there was excessive transdermal loss of water and in our cases absorption of urea.

We hope that our cases and those of Dr Garty will remind our colleagues that skin is not an impervious barrier.

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Vitamin D metabolites in idiopathic infantile hypercalcaemia

Sir,

We have further investigated two of the infants with idiopathic infantile hypercalcaemia described by Martin *et al*[1] and confirmed the presence of appropriate suppression of 1α hydroxylase activity in the presence of hypercalcaemia, suggesting intact feedback mechanisms.

As vitamin D supplements (400 IU/day) were withdrawn and a low calcium diet begun in case 1 the serum calcium concentration fell. Concentrations of 1,25-dihydroxycholecalciferol (1,25(OH$_2$)D) rose and 25-hydroxycholecalciferol (25-OHD) fell due to the withdrawal of supplements (Table 1).

Calcium load tests, modified from the protocol of Barr and Forfar,[2] showed an abnormal response when performed at 7, 13, 18, and 24 months in case 1 and at 22 months in case 2. Furthermore, 1,25(OH$_2$)D concentrations performed during the most recent load tests showed appropriate suppression in the presence of hypercalcaemia (Table 2), suggesting intact homeostatic mechanisms.

Our assay is able to distinguish between 1,25(OH$_2$)D$_2$ and 1,25(OH$_2$)D$_3$ and it would seem that 1,25(OH$_2$)D$_3$ is more tightly controlled than 1,25(OH$_2$)D$_2$. The significance of this observation is unknown as these metabolites have not previously been measured in children with this condition. Further studies will be necessary to confirm our findings.

Dr Martin suggested that the low concentrations of 1,25(OH$_2$)D seen in the patients with hypercalcaemia could be due either to appropriate suppression of 1α hydroxylase activity or to a reduced growth velocity. The results of the loading studies and the fact that the growth velocity of our first child did not alter with correction of the hypercalcaemia suggests that the former is a more likely explanation. Whether there is poor control of production of 1,25(OH$_2$)D$_2$ and whether this is important in the aetiology of the hypercalcaemia is an area for future study.

I thank Dr Barbara Mawer, Manchester University, for performing the assays.

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M E McGraw
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Table 1 *Reaction of serum calcium and vitamin D concentrations to withdrawal of vitamin D supplements in case 1*

	At diagnosis	*Time after treatment*		
		2 weeks	*4 weeks*	*7 months*
25-OHD (ng/ml)	48·6	53·5	40·6	30·7
1,25(OH$_2$)D (pg/ml)	31·0	38·0	47·0	69·0
Calcium (μmol/l)	3·16	2·38	2·47	2·44

25-OHD = 25-hydroxycholecalciferol; 1,25(OH$_2$)D = 1,25-dihydroxycholecalciferol.

Table 2 *Vitamin D metabolites during calcium loading in the two cases*

	Fasting	*Calcium loading (hours)*					
		0·5	*1*	*1·5*	*2*	*3*	*5*
Case 1							
Calcium (μmol/l)	2·44	2·77	—	2·86	—	2·79	—
1,25(OH$_2$)D$_2$ (pg/ml)	6	7	—	7		5	—
1,25(OH$_2$)D$_3$ (pg/ml)	63	55	—	53	—	61	—
Case 2							
Calcium (μmol/l)	2·53	—	3·37	—	3·23	3·15	2·79
1,25(OH$_2$)D$_2$ (pg/ml)	21	—	21	—	20	20	18
1,25(OH$_2$)D$_3$ (pg/ml)	60	—	57	—	56	47	34

1,25(OH$_2$)D$_3$ = 1,25-dihydroxycholecalciferol.

The diagnosis and management of food allergy

Sir,

In his article on food allergy Dr Cant discusses abnormal psychological reactions of some parents of children with food allergy but fails to mention similar problems in children who have grown out of the disorder.[1] My 6 year old son outgrew his cow's milk allergy two years ago and now eats a normal diet. Despite all our efforts to the contrary, however, he still eats his breakfast cereal without milk and his puddings without custard, and it has taken two years of intensive retraining to persuade him to eat ice cream. While this is not a great problem, I feel that other children will have more serious long term psychological effects from restriction diets for food allergy and this aspect has not been widely documented in the past.

Reference

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R J Welch
Newcastle General Hospital,
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Pulse oximetry in neonatal care

Sir,

The pulse oximeter, a fast non-invasive method of continuous arterial oxygen saturation monitoring, is beginning to be used in neonatal units as a prompt warning of hypoxaemia in the unstable baby. The device measures the absorption of selected wavelengths of light passed through a sample of living tissue from which the quantity of oxygenated and reduced haemoglobin can be calculated. The neonatal probe is designed to be wrapped around a hand or a foot. It is unheated and not adherent to the skin. We report an added use for this device.

A 620 g, 25 week old baby born in this hospital had moist friable skin. Even foam backed electrocardiogram electrodes caused trauma to the superficial skin layers, resulting in risks of introduction of sepsis and increased fluid losses. We anticipated a conventional heated transcutaneous oxygen sensor would do the same. We therefore monitored this ventilated baby entirely using the pulse oximeter (Ohmeda Biox 3700), placed around an upper arm and occluded from ambient light. This allows digital read out of heart rate and oxygen saturation, a graphic display of the pulse, and high and low alarms for all readings. This was used successfully for two weeks, producing no skin trauma and no complications and a reduced need for handling the infant. This device may reduce handling and skin trauma in the monitoring of heart rate and arterial oxygen saturation in immature infants with friable skin, who require neonatal intensive care. Direct arterial oxygen partial pressure monitoring, through an indwelling line, is also required to detect hyperoxaemia, as on two occasions this baby had an oxygen tension of 15 kilopascals when the pulse oximeter reading was 93%.

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Archives of Disease in Childhood, 1986, **61,** 1248–1249

Book reviews

Current therapy in pediatric infectious disease. By J D Nelson. £39·50 hardback. Blackwell Scientific, 1986.

This book is a compilation of personal approaches to the management of paediatric infection and as such is not intended to be 'a textbook of infectious diseases'. An extensive range of illness is covered, from that encountered by any doctor dealing with children—for example, otitis media, acute diarrhoea, and croup—to that seen with any frequency only by the specialist—for example, tularaemia and Lyme disease.

There is a loose overall format but a great variance in the amount of general background information with which each author invests his writing. This may leave the reader glossing over the obvious on the one hand and scurrying to standard works on the other to provide a base for the text. This is a book more for the doctor with a certain minimum of experience than for the student. The editor sees the book as the synthesis of the contributor's past instruction, personal experience, and assessment of the medical publications. There are thus no references. It is always of interest to hear how others deal with clinical problems familiar to oneself, but I found the absolute absence of references somewhat frustrating when stimulated by a comment to look up the source.

Overall, the book makes interesting and enjoyable reading, but I am doubtful of its usefulness to the general British paediatrician. At times I could not help feeling that parts of it were lacking in substance, and because of the array of diseases covered too little is often said of too much.

S P CONWAY

Child Health Behavior: a Behavioral Pediatric Perspective. Edited by N A Krasnegor, J D Arasteth, M F Cataldo. Pp 644: £49·10 hardback. John Wiley and Sons, 1986.

To what extent should British paediatricians be concerning themselves with developments in behavioural paediatrics? Is there any coherent 'behavioural pediatrics perspective' on child health behaviour as the title of this prolix volume suggests. Perhaps not, if we accept the view of the ultimate chapter's authors; to wit, it is 'an area ultimately defined by the activity of its participants.' Historically, the field of interest developed from three fairly distinct origins. Firstly, liaison psychiatry and child psychiatric theory and practice; secondly, psychosomatic medicine in adults; and thirdly, empirical research in experimental psychology, especially learning theory and principles of behaviour modification that derived from it. Contributions relevant to each of these aspects of behavioural paediatrics are included.

Intended to be a comprehensive assessment of the current state of knowledge about behavioural paediatrics, the book suffers from a lack of focus. For instance, a chapter on the philosophy of 'behavioural systems' rubs shoulders with an excellent review of the appropriate functions health education should play in schools. All in all, there are 26 chapters, but just one in three merits reading in depth. These include, besides that mentioned above, approaches to the control of childhood accidents, a critical review of campaigns to reduce smoking among adolescents, social and behavioural aspects of obesity, the primary prevention of hypertension, a biobehavioural analysis of the origins and management of childhood headache, problems in parental compliance with treatment, paediatric gastrointestinal disorders, strategies and future directions for research in behaviour management of paediatric problems, and issues concerning training in behavioural paediatrics.

Besides difficulties in maintaining a coherent focus of content, the book suffers from failing clearly to define its potential readership. Paediatricians may well become exasperated by endless 'conceptual models' and discussion on the 'theoretical underpinning of ecological sub-systems.' A more than passing acquaintance with the use of behaviour modification techniques is advisable before tackling the contributions by behavioural scientists. Clinical psychologists and child psychiatrists involved in paediatric liaison work may find it more to their taste. In conclusion, this could have been an excellent book at half the length, highlighting issues the contemplation of which would benefit those employed in general or community paediatric practice.

DAVID SKUSE

The Overactive Child. Edited by E A Taylor. Pp 269: £16·00 hardback. Blackwell Scientific/Spastics International Medical Publications, 1986.

This book from the Maudsley has taken on the task of critically examining what is truth and untruth and what is fact and fantasy in the world of hyperactivity. The result is a scholarly and objective book that leaves no stone unturned. While it is not light reading, there is an enormous amount of real information on a subject that has been surrounded by vagueness in definition and management.

GWILYN HOSKING

Diagnostic Paediatric Imaging—a Case Study Teaching Manual. By C M Hall, S Lingam. Pp 200: £29·00 hardback. Springer-Verlag, 1986.

This 'case study teaching manual' assembled by a radiologist and a paediatrician presents imaging material from 100 cases arranged in systems. Each case has three to five questions based usually on one or two images. Answers on the following page are of easy access (possibly too easy) with concise information and often further explanatory images. The imaging examples cover all the usual modalities except angiograms and nuclear magnetic resonance, and there seem to be no examples of intracardiac anomalies. The central nervous system is also probably under represented, with only four cases. Aspects tested cover not only powers of radiological observation but also a knowledge of relevant clinical matters as well as the choice of further imaging techniques to use. Some emphasis is laid on testing practical knowledge on performing radiological procedures—for example, barium enema for intussusception in case 19—and the choice of contrast material to use. Examination candidates need lists of differential diagnoses and this book has them—for example, conditions associated with hemihypertrophy, causes of osteoporosis, and causes of radial hypoplasia.

The answers are concise but some have further comments, though there are no references to read further. There is a good subject index.

Setting water tight questions is always difficult and experts might disagree on what was the diagnosis and what was the differential diagnosis in case 87, but the questions mainly avoid confusion.

In two cases my colleagues and I were unable to identify the lesion reported in the answer (a pneumothorax and a radiolucent area in bone) even after looking at the *x* ray pictures again, but I imagine there is an inherent problem in transposing *x* rays into print that makes them less clear than the original.

For myself, I enjoyed reading this book and learned a lot. For teaching in paediatric departments and for private study it will be a useful resource. Diploma in child health candidates are rarely shown *x* ray films, but this book will be useful for those taking part II of the MRCP examination in paediatrics. Presumably it will be similarly helpful to radiologists in training.

G MCENERY

Understanding Allergies. By M Steel. Pp 176: £5·95 paperback. Consumer's Association/Hodder and Stoughton, 1986.

Food Allergy—A Primer for People. By S A Bock. Pp 72: paperback. A J Publishing Co, 1986.

These are both good books about allergy and can be recommended to parents. Understanding Allergies' is easy to read, covers a wide field, is technically fairly accurate, though tends to emphasise the allergic aspects of atopic disease, and is marred only by a weak final section on complementary medicine. 'Food Allergy—A Primer for People' is confined to the subject of food allergy and is a distillation of the various diagnostic and therapeutic principles and techniques. It has a useful final section on controversial or unorthodox procedures.

T J DAVID

Inspecting the Newborn Baby's Eyes. By N O'Doherty. Pp 104: £75·00 hardback. MTP Press, 1986.

Professor O'Doherty comes over in his book as an enthusiastic and stimulating teacher, full of anecdote and incidental observation. At first, the title of the book seems very limiting as fundoscopy is almost entirely excluded and the level of examination suggested appropriate for the obstetric or paediatric senior house officer. On turning the pages, however, one is persuaded that almost all of neonatal disease may be seen by inspecting babies' eyes. The mainly coloured plates are very well reproduced but illustrate much that is only peripheral to the examination of the eyes, such as cryptorchidism, syndactyly, and a child with a hearing aid to illustrate deafness. Many show older infants or even adults.

Unfortunately, while being a delightful read for the experienced paediatrician and classicist (it is liberally sprinkled with quotations), the book is too eclectic and meandering for the learner. Where the slide collection was well provided rarities are well illustrated. In the brief section on eye infections, however, chlamydia is not even mentioned, and retinopathy of prematurity only just gets in, although the index refers us to illustrations of a retinoblastoma. At £75, it is only a suitable gift for the neonatologist who has everything.

RICHARD COOKE

Practical Paediatrics. Edited by M J Robinson. Pp 613: £24·00 paperback. Churchil Livingstone, 1986.

This is described in the foreword as the firs Australian textbook of general paediatrics. It is aimed mainly at undergraduates but is more comprehensive than most such British texts. Though the list of authors is large, including 38 Australians and one Malaysian, the style is consistent and readable and the approach practical and problem orientated. I particularly liked the chapters on genetics, the approach to the dysmorphic child, and growth and development and the section on social and preventive paediatrics. History and examination is not neglected and the chapter on the difficult topic of inborn errors of metabolism is a model of clarity.

The practical presentation can cause problems, such as the unsatisfactory siting of important topics like failure to thrive and fever of unknown origin in a miscellaneous penultimate chapter. Nutrition is dealt with rather skimpily, just six pages, including two on obesity and one that is a list of artificial milks.

These are, however, minor criticisms. I enjoyed reading this book and would recommend it to my residents reading for postgraduate examinations. It has a distinctive Australian flavour in morbidity and epidemiology data, in covering the problems of Aboriginal and Australian immigrant families, and even in mention of Agent Orange as a possible teratogen, but overall this book differs little from my practice and teaching in northern Scotland. I would suggest that a British edition with minor modifications would be a considerable competitor for our own textbooks.

P J SMAIL

Archives of Disease in Childhood, 1986, **61,** 1250

British paediatrics

Liver transplantation

A joint working party between the British Paediatric Association and the British Association of Paediatric Surgeons has recently reported its findings. The report reviews the history and present state of liver transplantation, comments on the related problems in children, and discusses the resource implications.

The first human liver transplantation was performed in 1963 and during the next 10 years over 600 transplants were carried out in 15 centres in Europe and North America. By 1983 it had been clearly shown that liver transplantation could prolong life in patients with severe liver disease for which there was no effective alternative treatment.

Professor Stazl's unit in North America has recorded a 70% one year survival in children, although 30% require a second transplant within that period. Surviving children have normal liver function and most of them show good catch up growth. The quality of life in survivors is good and most can resume their former activities. There are many fatal complications and current data are insufficient to allow full evaluation of survival beyond one year. The disorders for which liver transplantation has been performed in children include extrahepatic biliary atresia when standard surgery has failed, progressive cirrhosis due to α_1 antitrypsin deficiency, Wilson's disease that has failed to respond to chelation therapy, and certain types of glycogen storage disease.

The postoperative period of intensive care is about 14 days, during which there is a high risk of complications, particularly bleeding and problems in the biliary, pulmonary, renal, and cardiovascular systems. Early regrafting may be necessary because of thrombosis or rejection. Immunosuppression is still not satisfactory and increased susceptibility to infection is a major problem in children. The risk of long term malignancy has not yet been assessed.

The working party report quotes the recommendations of a National Institutes of Health consensus conference regarding the stages of liver disease in which transplantation should be considered. These are:

When death is imminent;

When irreversible damage to the central nervous system is likely to develop;

When the quality of life has deteriorated to an unacceptable level.

The resources needed for liver transplantation are considerable. The procedure can only be undertaken in tertiary care centres with an active transplantation programme. In addition to expert surgical personnel the transplant team must include paediatricians, hepatologists, psychiatrists, social workers, and a transplantation coordinator. Services such as tissue typing, immunology, pathology, radiology, and renal dialysis should be available.

The number of potential candidates for transplantation in children is not known. The working party estimates that at least 70 children die each year in the United Kingdom from disorders for which liver grafting has been effective, but it is not known how many of these might have major contraindications to the operation.

There are currently three centres in the UK providing an active liver transplantation service. The Cambridge/King's collaborative service has carried out 230 transplants (up to July 1985), of which 26 were in children. The Birmingham service has transplanted 30 patients, including two children. The Royal Free Hospital started its service in 1981 and has so far undertaken only eight transplants, none in children. The Secretary of State has agreed that the Cambridge/King's and Birmingham services should receive central funding for 1986–87.

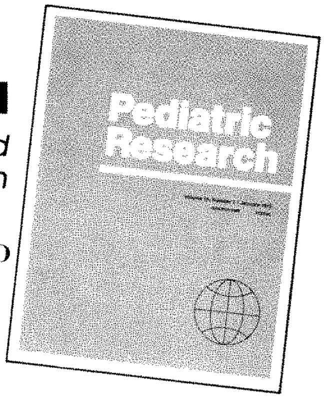
The main conclusions of the working party are that:

Liver transplantation is now a realistic form of treatment for which there is a demonstrated need in the UK.

Paediatric services should be developed in conjunction with transplantation services for adults. The children should be cared for in children's units by children's trained staff.

At this stage paediatric services should be developed only in two centres, Cambridge/Kings's and Birmingham.

A register of children with chronic liver disease and metabolic disorders that may require liver transplantation should be set up at the department of child health at King's College Hospital.



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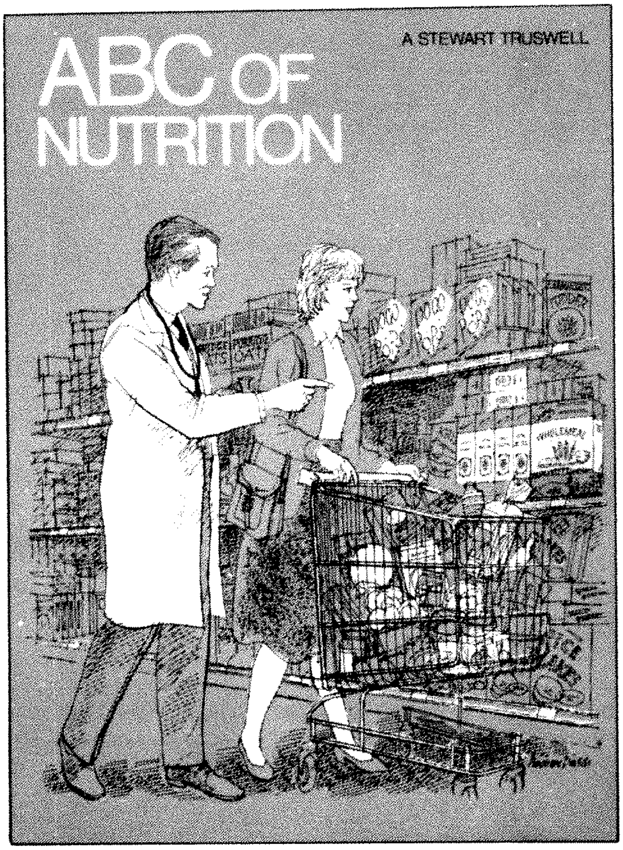

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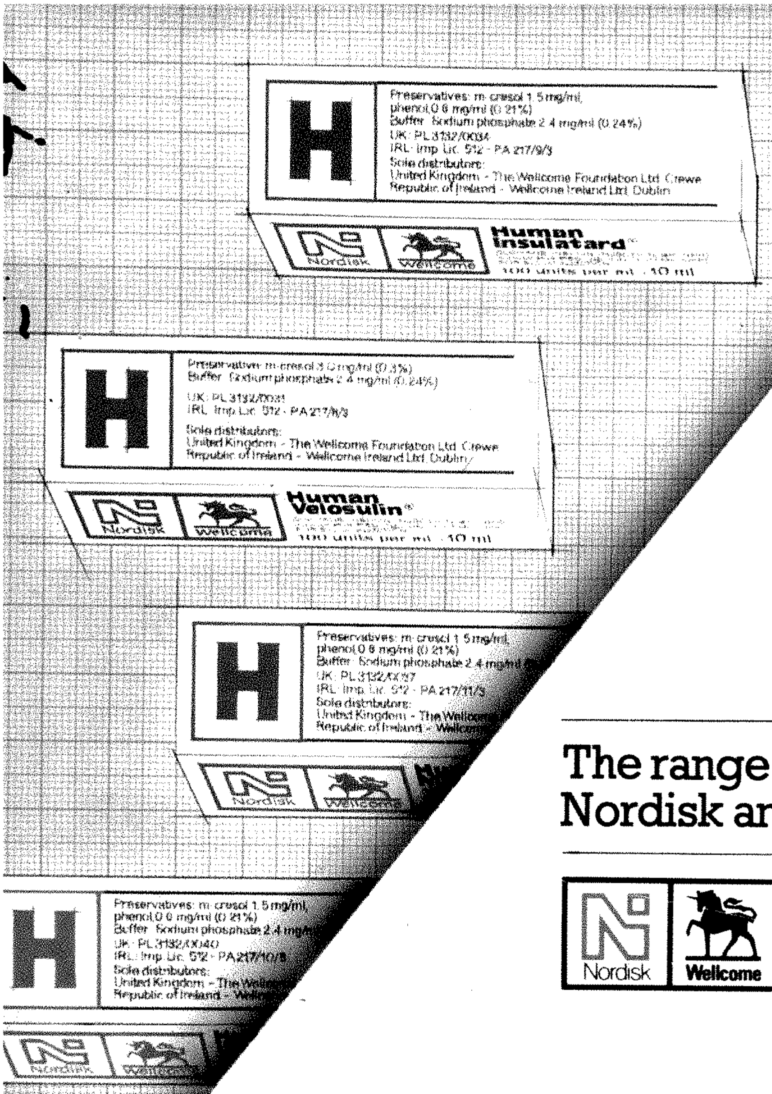

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